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of
NORTH AMERICA

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DECEMBER, 1942

VOLUME 22—NUMBER 6

PHILADELPHIA NUMBER

THREE YEAR CUMULATIVE INDEX

Volumes 20 21 and 22

(1940 1941 and 1942)

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TREATMENT OF FRACTURES AND BONE AND JOINT SURGERY WITH THE STADER REDUCTION AND FIXATION SPLINT

C M SHAAR MD FACS†

d

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TREATMENT of fractures has received serious consideration by many but while definite progress has been achieved from time to time it can nevertheless be said that this branch of surgery has not kept pace with other surgical developments. The many advances in fracture treatment that have been made have been accomplished chiefly because surgeons with unusual mechanical talents have recognized the correlation between actual surgery per se and the strains and stresses that must be overcome and maintained to reduce fractures effectively and to hold this reduction until solid bony union has occurred. We might therefore visualize the management of fractures as a mechanical problem but one that must incorporate the surgeon's knowledge of the anatomical structures involved—the soft tissue as well as the skeletal the systemic as well as the local—and also a thorough knowledge of the process of bone repair.

The present book is a contribution to the literature of the subject of fractures and bone and joint surgery. It is a book that will be of interest to the surgeon and the student of surgery. The book is written by two of the leading authorities in the field of orthopedic surgery. The authors are C M Shaar and Frank P Kreuz. The book is published by the American Medical Association. The book is available in paperback and hardcover. The price of the book is \$4.50. The book is available from the American Medical Association, 535 North Dearborn Street, Chicago, Illinois. The book is available from the American Medical Association, 535 North Dearborn Street, Chicago, Illinois. The book is available from the American Medical Association, 535 North Dearborn Street, Chicago, Illinois.

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which were similar in principle to those used by Schantz and later by Riedel⁷ in femoral osteotomies and used successfully in this country by Anderson⁸ ¹¹ in treating fractures of the femur.

During the period of transfixation of fractures to eliminate the necessity of continuous traction efforts were also being made to eliminate the necessity for the use of plaster itself.

Although Codivilla and others ^{1 12 11} bridged Steinmann pins with external metal bars the method never became popular because of the through and through pinning required. Lamare in a description of angular pins placed through the outer and inner cortex only which he bridged in units by means of metal bars opened the approach to an external mechanical method of treating fractures which could be applied to one aspect of the limb only thereby eliminating the objectionable through and through pinning and plaster.

Recognizing the greater necessity for the elimination of plaster in the treatment of fractures in dogs because of plaster soilage cast destruction by the patient the difficulty of applying plaster and maintaining immobilization in the dog as well as the too often occurring gangrenous sequelae Stader ⁹ ³ developed a unique device for the treatment of fractures in which he combined mechanical reduction and subsequent immobilization in a single compact unit.

Using the Stader reduction splint Lewis Breidenbach and Stader have in the past five years treated more than fifty acute fractures of the lower leg in humans most of them in Bellevue Hospital in New York City. Their results were so outstanding as to interest us seriously in the continuance of this work. In addition Stader and his associates have in the past ten years treated more than twelve hundred fractures in the dog a type of experience few of our present day innovations in the treatment of fractures enjoy.

Stader first presented the advantages of his splint to us in December 1941. Since that time we have used it in over forty cases of various types of fractures and orthopedic problems. We realize that this small number of cases and the short time interval do not speak for a final evaluation of the method.

HISTORICAL APPROACH

The foundation of the modern advance in the treatment of fractures by means of externally controlled skeletal fixation was laid by Codivilla, who first used the principles of the Steinmann pins. These he connected with external bars without the use of plaster. After the advent of the Steinmann pin various interpretations of its adaptation especially with regard to external fixation of the pin with plaster or mechanical devices were published by many. The literature pertaining to the use of the pins or screws inserted into bone fragments above and below the fracture for the purpose of external fragment reduction control and subsequent fixation is so voluminous (see Supplementary Bibliography) that it may be well to discuss briefly in general the various methods so that the student of fracture treatment can visualize more clearly the evolution of the advancements that have taken place.

Until the principles of the Steinmann pin were described by Codivilla in 1904 the treatment of fractures meant the use of plaster of paris or various methods of external traction and countertraction.

With the advent of skeletal traction popularized by Steinmann the next noteworthy advance was the incorporation of the Steinmann pins or Kirschner wires in plaster for the so-called transfixation of the fragments. Bohler's contribution during this phase was outstanding. His use of a simple reduction frame and screw traction apparatus in conjunction with pins or wire introduced a new era in accepted fracture treatment. His persistent efforts and successes were chiefly responsible for the gradual elimination of pin phobia held then by many surgeons and still retained by some today. His simple reduction frame is the basis for many of the elaborate devices now offered the traumatic surgeon.

To overcome the necessity of through and through pins which obviously cannot be used in the upper femur Clayton Parkhill in 1897 inserted screws from cortex to cortex and then connected the screws with an external clamp in treating difficult fractures of the femur as well as other long bones. Lamare described half pins placed at an angle to each other

tion which occurs at the fracture site during the process of bone repair. The impacting adjustability of this splint without fragment disalignment marks it as a device far in advance of others.

The complete articular freedom above and below the fracture afforded by the Stader splint decreases to a minimum the joint disabilities so often observed where joints have been immobilized over long periods of time. The active motion possible enhances circulation, reduces soft tissue atrophy, favors early union, adds greatly to the patient's comfort and in most instances renders the patient ambulatory from the first postoperative day. This last mentioned advantage is of special significance in wartime as it permits evacuation of patients from danger zones either by themselves or with a minimum of assistance.

The structural qualifications of the Stader splint permit full weight bearing and it can be so securely locked into position that postoperative displacement is impossible. Recently Haynes reported an external mechanical splint. Reduction however must be performed with a separate reduction device as is the case with the Roger Anderson apparatus.

Pin Seepage

Although the Stader splint does not eliminate pin seepage completely, we have reason to believe that this has been reduced to a negligible factor. There appear to be several factors involved in the production of pin seepage, the most important of which are stated below.

1. A not yet fully explained electrical phenomenon evidenced by galvanometric readings is noted when two or more pins are bridged by metal bars of different electrical qualities such as would be the case in any mechanical external fixation device. Electrolysis of the tissues as a factor in pin seepage suggested itself to Stader in his fracture work on animals. He therefore incorporated in his device an electrically insulated pin bar to interrupt this electrical disturbance. When contact of the pin with the external bar is interrupted by such an electrical insulator, galvanometric readings at this hospital indicate that there is a definite electrical

employed but we feel that the present war emergency requires one to bring before the medical profession and the armed services as quickly as possible any new method of merit for caring for the injured. We feel that this method is far superior to any other previously employed.

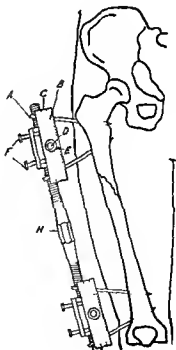
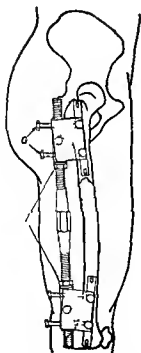
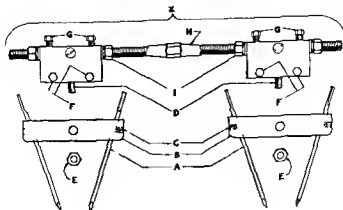
ADVANTAGES OF THE STADER REDUCTION SPLINT

To us the outstanding advantages of the Stader reduction splint are the simplicity of the reduction maneuvers coupled with its compactness its relatively light weight and the fact that it is applicable to one aspect of the fractured limb only. The fact that the adjustable connecting bar assembly remains *after reduction and then acts as the splintage* has the further advantage of enabling one to make any desired adjustments at the bedside without removing the patient to a special bulky reduction frame. This advantage is of special value for example in leg lengthening operations and other operative procedures met with in bone surgery.

With the Stader splint therefore it is entirely feasible and may often be desirable *aboard ship and in field hospitals* to apply the splint as a reduction and immobilizing agent. If secondary adjustments are necessary they may be performed later in a base hospital under fluoroscopic control without subjecting the patient to any further surgical procedures.

We subscribe fully to Bradford's statement wherein he points out the shortcomings of definite skeletal fixation. He states: *Any form of treatment that tends to fix fracture ends in a position of distraction cannot fail to delay and prevent union since the pins allow no backward slipping and their position is locked in place.* Mechanical fixation should become a treatment of persistent controlled impaction which offers an advantage over any other method available except those suitable for walking casts. Lambotte anticipated this principle over forty years ago.

Bohler's success with walking calipers in tibial fractures is due chiefly to the continuous impaction of the fragments obtained. No external or internal mechanical device examined by us with the exception of the Stader reduction splint permits week by week impacting to overcome the bone absorp-



Figs 465 466—Sh m c d w g f S d d tu pl t A Stai
 l ss l p B P blk C S -sc w l k g p D H g b l E
 N tr h g pin block t h g b lt. F M d l t rsl dj t g w
 C A p dj g ew H Adj bl in g b l
 l k l k g b H Z Adj bl g b mbly

disturbance present but that it remains static. Further studies are in progress with special electrical measuring devices in an attempt to evaluate this problem.

2 The application of various bulky dressings to the pin sites tends to macerate the contiguous soft structures around the pins.

3 Where the pins penetrate through thick soft structures subsequent movement between these soft structures and the pins has a tendency to increase pin seepage. This is of no importance as in every case under our observation drainage subsided in a few days.

4 There is practically no pin seepage when the pins are properly applied and held firmly in place. Seepage is more evident when pins are inserted in cancellous or demineralized bones or when the pins are improperly seated in cortical bones. By improper seating we mean failure to place the pins through both cortices or carelessness in placing the pins which results in the diameter of the channel being larger than that of the pin itself usually the result of unsteady pressure when drilling the pins.

In our series of over forty cases (using 160 half pins) pin seepage was observed in conjunction with less than 10 per cent of the pins. The seepage subsided in a few days without any irritation of the bone or soft tissue and in no case was there any evidence of osteomyelitis around the pins.

5 The introduction of pins into previously traumatized or devascularized soft tissues tends to ward greater pin seepage. This seepage decreases in proportion to the tissue healing. In our series of cases we have not had any pin seepage of serious consequence and no complications have occurred as the result of the use of pins.

APPLICATION OF THE SPLINT

The actual application of the Stader reduction splint is not difficult. Special stainless steel pins *A* (see Figs 465, 466 and 468) sharpened similar to a trocar and of suitable size are inserted through the pin guide holes in pin bars *B* and are drilled into their proper position either by hand or with the aid of a flexible shaft drill (Fig 467) which may be either

sembly is properly placed. The pins are then locked into the pin bar with an easily operated universal wrench (Fig. 468).

As a rule the pins are placed as near to the bone extremities as is consistent with the anatomical structures involved. This facilitates both reduction and fixation and in most instances avoids the insertion of pins near or into the fracture site.

After both upper and lower pin assemblies have been placed approximate reduction and alignment of the fragments are secured by hand. While this approximation is maintained by the surgeon an assistant attaches the adjustable connecting assembly bar (Fig. 465, Z) into position and tentatively tightens all the adjusting screws (*F* and *G*, Figs. 465, 466) with the fingers only. Exact reduction is now obtained by means of wrenches activating the various mechanical adjustments illustrated in the diagrammatic drawings (Figs. 465, 466).

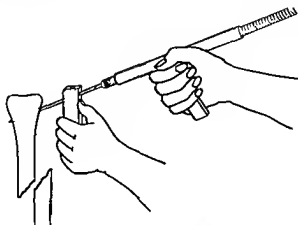
The actual application of the pins is carried out in the operating room with or without *fluoroscopic guidance*. It may easily be carried out aboard ship or in the field hospital.

Fluoroscopic guidance for *reduction* is of great value or a series of x-ray plates may be made. In transverse fractures after fragment alignment has been secured firm impaction is produced by activating bar *H* (Figs. 465, 466) after which lock nuts *I* are tightened to prevent rotational displacement. In oblique fractures impaction is obviously not feasible but side to side pressure is obtained by properly adjusting screws *G* or *F* as the case may demand.

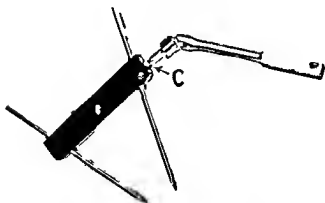
As a final procedure after proper reduction and impaction have been secured adjusting screws and lock nuts are checked to make sure they are tight. Thus then locks the reduction mechanism and the instrument now assumes the role of a splint.

The following cases are presented not only for their interest value but to show the wide range of adaptability of this splint in the treatment of fractures as well as in various orthopedic problems.

hand operated by an assistant or motor driven as in the Mueller bone engine



F 467—Fl uel h f drill



Fg 468—Un rsal w h f l l g p ns in p b

The upper p n assembly is first placed in proper position then the lower part of the extremity is corrected for rotational displacement if present after which the lower p n as

[illegible]

Formulation

[illegible]



Fig 4/9 (Ca I E P) - C mp d f tu f gh b j ct
f d d l h d A S d d plint ppl d B P p
y film C P p ra y film D F l l

anesthe a Fre active motion of the extremity was permitted but no weight bearing because of the crushing injury of the left foot. No p n seep ge or complications ensued and the splint was removed May 12 194. The final x ray shows a firm bony union.

FRACTURES OF THE SHAFT OF THE TIBIA

The Stader splint is ideal for fractures of the shaft of the tibia especially those that are compounded comminuted or associated with severe soft tissue injury. In transverse fractures which so often are the cause of delayed union or non union the splint also offers a very important advance over the usually accepted forms of treatment because it allows for proper *controlled impaction* of the fragments by means of the rigid adjustable connecting bar of the splint. As stated before our observations in these cases are in accord with those of Bradford. Technically speaking distraction of the fragments by any means whether by mechanical appliances or by transfixation in plaster is the same as overextension which will always produce delayed union or no union at all.

Controlled impaction to us is a definite answer to the problem of delayed union or nonunion in transverse tibial fractures. In fractures that are compounded comminuted or associated with extensive soft tissue injury the Stader splint is ideal because it allows absolute rigid fixation of the fragments while treating the soft tissue. The wound excision or debridement is thereby simplified and additional injury to the soft tissue resulting from traction and tissue handling including the use of bone holding forceps is obviated or decreased to a minimum. The splint also allows free access to the wound and direct observation to determine early signs of gas infection or other complications.

There were five cases of acute fracture of the shaft of the tibia in three of which the fractures were compound and in one osteomyelitis as present. The treatment in three of these cases has been completed and firm bony union with complete function has been obtained two patients are still under treatment with the splint and show bony union but the union is not yet firm enough to allow removal of the splint. (See Table.)

CASE I (F 469) — E. P. a forty eight year old male suffered a compound fracture of the right tibia at the junction of the middle and lower thirds of the shaft. Rush gangrene of the foot with comminuted fractures of all metatarsals bones. The Stader reduction splint was applied on February 22, 1942 under local

CASE II (Fig 470) —C K a twenty five year old male had a compound fracture of the tibia at the junction of the middle and lower third The Stader splint was applied on March 20 1942 one day after the accident Weight bearing was permitted from the first postoperative day There has been no muscle atrophy or pin seepage after fourteen weeks immobilization

Time of Fracture of the Shaft of the Tibia with Short Fragments

In order to allow free active motion of the adjacent joints it is possible to incorporate fragments as little as 2 inches

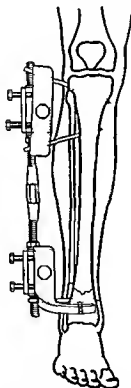


Fig 471 —Diagram of a right leg splint for short fragments

from the joint in the Stader reduction splint by means of a special right angled pin unit (Fig 471)



Fig 40 (Case II C. K.)—Compo d fra tu f b l cr f
 muddl and l th d A S d d cu spl ppl d B X ra film
 th spl pl C Ph ograph k f f rtee w ks mm bl za
 n, sh g l k f m scl rophy d p seepag

CASE II (Fig 470) —C K a twenty five year old male had compound fracture of the tibia at the junction of the middle and lower third. The Stader splint was applied on March 20 1942 one day after the accident. Weight bearing was permitted from the first postoperative day. There has been no muscle atrophy or pin seepage after fourteen weeks immobilization.

Treatment of Fractures of the Shaft of the Tibia with Short Fragments

In order to allow free active motion of the adjacent joints it is possible to incorporate fragments as little as 2 inches

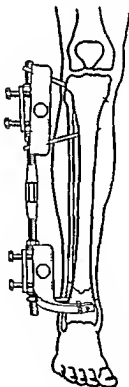
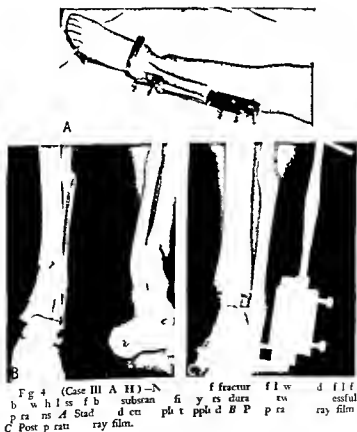


Fig 471 —Diagram of special right angled splint for short fragments from the joint in the Stader reduction splint by means of a special right angled pin unit (Fig 471)

There were three cases of fractures of the tibial shaft with short fragments—two with a history of previous osteomyelitis nonunion and loss of bone substance and one with active osteomyelitis. All are under treatment at the present time and show excellent progress.

CASE III (Fig. 472).—A. H., a sixty-two-year-old male, presents a nonunion of a fracture of lower end of left tibia and lo



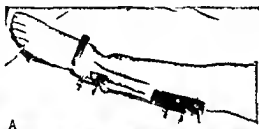
of bone substance of five years duration. He had had two previous operations on the leg and the other above



Fig 473 (Ca IV P H) - N m f fractu of ppe third of
 b h i f perau A S d d cu pl pph d B
 P pe y film C P p u ray film D R t x ray Leg
 pport d plast pl t.

There were three cases of fractures of the tibial shaft with short fragments two with a history of previous osteomyelitis nonunion and loss of bone substance and one with active osteomyelitis. All are under treatment at the present time and show excellent progress.

CASE III (FIG. 472) — A H. a sixty two year old male presented nonunion of fracture of lower end of left tibia and loss



A



B



FIG. 47 (Case III A. H.) — A patient with a history of previous osteomyelitis and loss of bone substance of five years duration. He had had previous operations including a sliding graft and the other a bone

of bone substance of five years duration. He had had previous operations including a sliding graft and the other a bone

customary to delay at least six to twelve months after the osteomyelitic process had subsided Orr however successfully plated compound fractures and recently McBride used

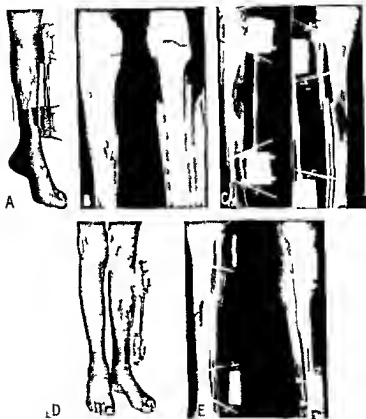


Fig 474 (Case V C T) - Compound fracture of tibia and fibula. A. Immediate postoperative view. B. Postoperative view showing the splint. C. Postoperative view showing the splint. D. Postoperative view showing the splint. E. Postoperative view showing the splint.

an osteoperiosteal graft under a plate and obtained union in cases of old fractures with nonunion and osteomyelitis. We believe that their success was due mainly to the rigid im-

plating operation, and both were followed by osteomyelitis and extrusion of the graft. The Stader reduction splint was applied on May 28, 1942, and a full thickness tibial graft was inserted with no internal fixation.

Old Fract. of the Sh. ft. f. th. Tb. with L. ss. f. B. ne.

Bone grafting of the tibia is greatly facilitated by first applying the Stader reduction splint allowing rigid control of the fragments during the operation as well as firm impaction of the graft so that no added internal fixation of the graft is required. There were five cases in which bone grafts were applied to the tibia with the aid of the splint.

CASE IV (Fig. 473).—P. H., fifty-three year old male had lost 4 inches of the upper third of the tibia following three unsuccessful operations for nonunion. The Stader splint was applied on February 10, 1942. During the operation it was possible to lift up the entire leg by grasping the 7 inch full thickness graft with a forceps, without any internal fixation of the graft itself. The splint was removed on May 18, 1942, at which time clinical and x-ray evidence of beginning bony union was present. The leg was then supported in a plaster splint.

Compound Fract. of the Tb. with O. t. my. i. t.

The Stader reduction splint probably has its finest adaptation in the treatment of compound fractures.

CASE V (Fig. 474).—C. T., a forty-nine year old male suffered a compound fracture of the middle third of the tibia. Following the immediate insertion of two plates the patient developed osteomyelitis with sloughing of the soft parts and extrusion of the plates in the wound. On March 9, 1942, one month after the fracture a Stader splint was applied, the plates removed and the bone thoroughly debrided. The wound was packed with sulfanilamide and vaseline gauze. On the second postoperative day the patient was ambulatory and guarded weight bearing was permitted. His convalescence was uneventful although painful during the first few weeks. In spite of four months immobilization no pin seepage was present.

Old Fract. of the Tb. with N. a. d. O. t. my. i. t.

It was always taken for granted that any bone grafting was contraindicated in the presence of osteomyelitis and it was

mobilization of the part. Because of this we decided to use the Stader reduction splint in conjunction with full thickness tibial inlay grafts in these cases. We have three such cases under treatment at the present time all showing excellent progress. The final results will be published at a later date. A careful search of the literature reveals no previous attempt to treat such cases by means of external mechanical fixation alone without additional internal fixation of the graft.

CASE VI (Fig 475) — H. G. a forty five year old male had an old compound fracture of the upper third of the left tibia of two years duration. He was treated at first by bone plate which sequestered with loss of 2 inches of tibia. Recently he suffered a fracture of the fibula with an acute flare up of osteomyelitis and copious drainage. The Stader splint was applied May 8 1942 and a 5 inch full thickness tibial graft was inserted without any internal fixation. A remarkable convalescence ensued with free motion of the leg without pain or febrile reaction and with subsidence of drainage in three weeks.

FRACTURES OF THE OS CALCIS

Using the principles as set forth by Bohler we have used a modified Stader reduction splint (Fig 476) in the treatment

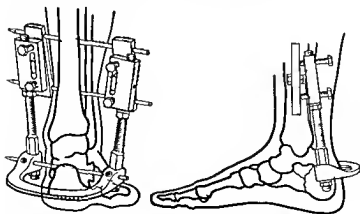


Fig 476—Diagram of modified Stader calcis splint

of fractures of the os calcis. No plaster immobilization is required. Tangential traction is secured and maintained with



F 475 (Ca VI H G)—Old mpo d fra f pp hrd f
 l f ribia f tw cars d ratu R fractur f fib l w th cu ost o-
 my litu d S d red cu spl p l d B P pera ray film C
 Post perati ray vi w

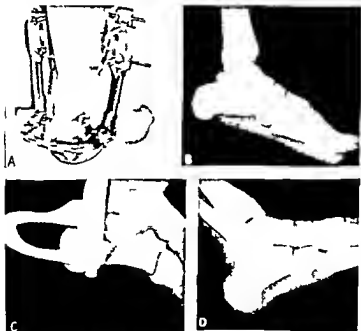
applied on March 24 1942 and removed on May 19 1942
Guarded weight bearing was allowed from the third postoperative day



Fig 478 (Ca VIII M W)—Fracture of femur distal end. Anteroposterior and lateral radiographs. A Splint applied. B Postoperative radiograph. C Postoperative radiograph. D Anteroposterior radiograph.

absolute rigidity at the same time allowing for necessary impaction and secondary adjustments as desired by a simple adjustment of the turnbuckle or screws. After the reduction of the shortening and the disparity of the tuber joint angle necessary compression of the os calcis is easily performed with the Bohler os calcis clamp without interference.

We have three cases of fractures of the os calcis treated by this method. The reduction was very simple and rapid and only one case required slight secondary adjustment to obtain an exact anatomical result.



F 47 (Ca VII J P) Fractur f l f os cal A S d os calci
pl ppl d B P p ra ra tilm C P st pe ray film D
I al res l

CASE VII (F 47) — J P t e t v s n year-old m l
as s en ith a fra ture of the left os cal Th t l r j t
angl as redu ed t ab t 5 degre s a d th as m d ate
ide g present The m difi d St de reduct spl t

applied on March 24 1942 and removed on May 19 1942
 Guarded weight bearing was allowed from the third postoperative day



A



C



Fig 478 (Ca VIII M M) -F
 1 Pl ppl d B P p
 D A n po n view

tu f right cal A S d
 ray film C P t p ray film

CASE VIII (Fig. 478).—**M. M.** a thirty-eight-year-old male presented a fracture of the right os calcis. There was considerable reduction of the tuberosity angle and moderate widening. Reduction was performed on June 16, 1941, eight days after injury. Exact anatomical reposition of the fragments was obtained. Guarded weight bearing was allowed from the second postoperative day.

This method of reduction and fixation for fractures of the os calcis by the Stader apparatus exceeds any method we have ever used.

FRACTURES OF THE SHAFT OF THE FEMUR

Fractures of the shaft of the femur on board ship and in field hospitals offer a very difficult problem because of the lack of and inadequacy of the usual bulky reduction armamentaria required. Treatment by continuous traction is impracticable in most instances. Treatment by plaster immobilization is difficult and unsatisfactory. The Stader reduction splint offers a ready solution to this problem. While this splint is comparatively small and compact structurally it is strong enough not only to maintain the reduction but also to allow some weight bearing.

CASE IX (Fig. 479).—**W. J.** a thirty-two-year-old male was found to have a transverse fracture of the shaft of the right femur at the junction of the upper and middle third complicated by scab injury from a directly crushing type of trauma. The Stader splint was applied on December 16, 1941, and removed on March 20, 1942. There was clinical evidence of good bony union.

Mild Fracture of the Shaft of the Femur

We feel that the Stader reduction splint has its application in the operative correction of various fracture deformities of the shaft of the femur. Day to day control of the osteotomized fragments permits gradual femoral lengthening as well as correction of the varus and other deformities.



Fig 479 (C IX W J) — T f f h f f ght f m
 l f pp d d m d d r i A Th S d d t pl
 ppl d B P p ra film C P pera ray w— ri
 post ri D Pos p y ew—l ral

CASE X (Fig 480) — N M a forty five year old male had a se enteen year old malunit d fracture of the shaft of the rght femur ith marked varus deformity and shortening of 2 1/2 nches The Stader reduct on splint was applied on June 16 1942 and a lo g oblique osteotomy of the mid shaft of the femur was performed Part al correction of the varus deformity was obta ned at the t me of the operati n Bi v ecklv adjustments



A



Fig 480 (Ca \ N M) - M I m d fra tu f h f f righ f m
 f se) rs d ra Sh rt m g f 24 h was p es A
 S d d spl ppl d B P pera ray film C \ ray k
 tv k pos pera h
 f r further ru co ct o nd f mo al le gthe ng re p r
 formed at the beds de See th v ay film tak n two v ecks post

operatively In the first two weeks $1\frac{1}{4}$ inches of lengthening was obtained

ARTHRODESIS OF THE KNEE JOINT

Transfixation of the knee joint by means of the Stader reduction splint permits visual control of the bone ends and forceful impaction thereof before the wound is closed The uninterrupted impaction and fixation by the splint favors earlier arthrodesis



Fg 481 (Case VI M E) -Transfixa f l j int rthritis by
ans f h S d d pl t. A Th kn po m val f h
pl B Pre pera rav film C X ray vi w tw m ths l t

CASE XI (Fig. 481) — M. E., a forty-eight year-old male, was seen with a severe infectious arthritis of the knee joint of eleven years duration. The St. der splint was applied December 22, 1941, and permitted to remain for seven weeks.

PATHOLOGICAL DISLOCATION OF THE HIP

During this series of cases we were confronted with a pathological dislocation of the hip in an elderly man who had

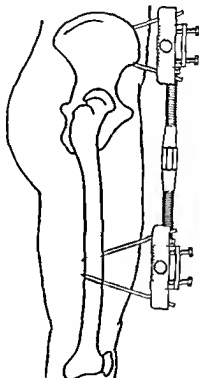


Fig. 48 — Diagram of the St. der splint for transfixation of the hip joint.

already been treated in a plaster spica for three months. He had a staphylococcus septicemia and a septic hip joint. It was necessary to remove the cast because of the formation of multiple pressure sores and severe pain incident thereto.

There was a recurrence of the dislocation with marked febrile reaction following the removal of the cast. The patient was markedly emaciated and desperately ill. It was impossible to treat him in extension or place him in another plaster cast. Confronted with this problem we elected to immobilize the hip by the use of the Stader reduction splint. The hip was therefore transfixed from the wing of the ilium to the mid shaft of the femur after reduction of the dislocation. A careful search of the literature reveals no previous attempts to immobilize the hip joint by means of a mechanical device bridging from the ilium to the femoral shaft (see Fig. 482).

CASE XII (Fig. 483) — H. H., a forty-eight year old male presented the findings above described. The Stader splint was applied April 24, 1942, the accompanying photograph being taken



Fig. 483 (Case XII) — H. H. — 48 y. old male. Hip dislocation. Stader splint applied April 24, 1942. Photograph taken April 24, 1942. (A) Hip dislocation. (C) Hip dislocation after reduction and fixation with Stader splint.

ten weeks later. During these ten weeks patient could be moved but not for massage and passive motion, and treatment of

pressure sores with minimal pain and temperature reaction. His general condition began to show steady improvement from the first day the splint was applied.

FRACTURES OF THE SHAFT OF THE HUMERUS

Fractures of the humerus have been treated successfully by many methods practically all of which however depend upon some form of joint immobilization—either above or be-

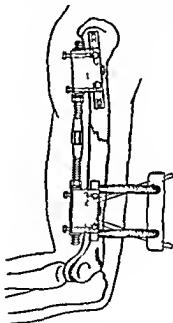


Fig 454—Diagram of the Stader humeral splint

low the fracture or both. Joint immobilization in these cases often produces prolonged disability. Therefore any method of treatment which eliminates the necessity for immobilization of the joints would seem to offer a distinct advantage. The Stader reduction splint not only allows us to treat fractures of the humeral shaft with free adjacent joints but in addition permits more accurate reduction and firmer fixation. The rigid fixation with this splint also decreases the tendency



Fg 485 (Ca NIII L B) -Tra nec f f th m d-sh f f
 h h m ru A Th S l h m l pl ppl d B P p)
 film C P pe) m d)

pressure sores with minimal pain and temperature reaction. His general condition began to show steady improvement from the first day the splint was applied.

FRACTURES OF THE SHAFT OF THE HUMERUS

Fractures of the humerus have been treated successfully by many methods practically all of which however depend upon some form of joint immobilization—either above or be-

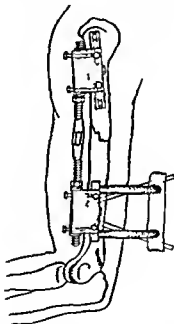


Fig. 494—Diagram of the Stader humeral splint.

low the fracture or both. Joint immobilization in these cases often produces prolonged disability. Therefore any method of treatment which eliminates the necessity for immobilization of the joints would seem to offer a distinct advantage. The Stader reduction splint not only allows us to treat fractures of the humeral shaft with free adjacent joints but in addition permits more accurate reduction and firmer fixation. The rigid fixation with this splint also decreases the tendency

towards excess callus formation which in turn not infrequently encroaches upon the radial nerve

A modified type of the Stader splint (Fig 484) is presented because of its greater adaptability for fractures of the shaft of the humerus in which the upper pin assembly is applied to the lateral aspect of the arm and the lower pin assembly applied to the posterior aspect of the arm. This arrangement permits the connecting bar to be applied parallel to the shaft of the humerus rather than obliquely as would otherwise be necessary

There were three acute fractures of the shaft of the humerus one badly comminuted extending throughout the entire mid portion and upper third with extensive swelling and hematoma one severely compounded in the mid shaft with severe traumatic gangrene of the triceps muscle and associated compound comminuted fracture of the elbow joint and shaft of the ulna and one acute transverse fracture of the mid shaft

CASE XIII (Fig 485)—L. B. a twenty five year old male had a transverse fracture of the mid shaft of the humerus. A modified type of the Stader splint was applied on July 5 1942

CASE XIV (Fig 486)—D. O. a fifty two year old male as seen with malunion of the mid shaft of the humerus of six months duration. Six months of plaster immobilization had caused stiffness of all the joints from the tips of the fingers to the shoulder. The Stader reduction splint was applied in February 4 1942 the eburnated ends of the fragments were freshened and the fracture reduced and firmly impacted under direct vision. Firm bony union resulted and the splint was removed at the end of three months

FRACTURES OF THE SHAFTS OF THE RADIUS AND ULNA

The reduction and the maintenance of fixation of fractures of both bones of the forearm are readily accomplished by this splint. We have applied it to the following cases

CASE XV (Fig 487)—S. N. a thirty year-old male presented a transverse fracture of the shaft of the radius at the junction of the middle and lower thirds with typical anterior displacement



F 486 (Cas. NIV D O) - Mal f m d h f f h m ru f su
 m th dura A Th Scad h m ral pl ppd B P pera
 ra film C Imm da l post pera D Th m h l



Fig 488 (Case No. 111 C M) - Fracture of the radius and ulna. B Postoperative radiograph film.



Fig 487 (Ca XV S N)—Transverse fracture of radial shaft, middle third with distal fragment displaced laterally. A Standard plaster cast applied. B Postoperative result. C Postoperative result with distal fragment in position. D X-ray of forearm.

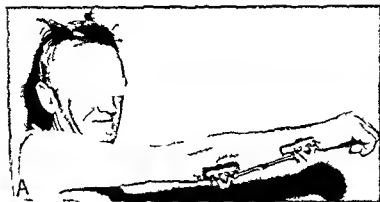


Fig 489 (Ca VII W W)—M l m d fractu f pp th d f
 gh l d d loc n f h d f rad A Stad d cu n
 pl Pl d B P cooperati x ray film C Post perati ray vi w

of the distal fragment and distal radio ulnar joint displacement. The Stader splint as applied on March 1, 1942, followed by free active use of the extremity from the first postoperative day. He was able to carry a 40 pound suitcase on the first postoperative day without pain. The splint as removed on May 29, 1942. Firm bony union had resulted with stiffness of the joints, atrophy of the muscles or weakness of the arm.

CASE XVI (Fig. 488).—C. M. a twenty five year-old male suffered a fracture of the radius and ulna in the mid shafts. Splints were applied to the radius and ulna on April 14, 1942. Free active use of the arm was possible from the first postoperative day. Pronation and supination were unrestricted. The radius splint as removed on May 27, 1942, and the ulna splint on June 28, 1942. Firm bony union had resulted and the patient's returned to full active duty on July 17, 1942.

Modified Fracture of the Radius and Ulna

The Stader splint offers the same advantages in operations on the radius and ulna as it does in operations on the lower leg, namely, rigid control of both fragments during and after the operation, elimination of internal fixation and securing of the graft when used, and free mobility of the adjacent joints. There were three unusual representative cases so treated.

CASE XVII (Fig. 489).—W. M. a forty six year-old male presented malunion of a fracture of the upper third of the right ulna and anterior dislocation of the head of the radius. A Stader splint was applied on June 2, 1942, the head of the radius was removed, the ulna osteotomized at the fracture site and the fracture reduced and directly closed by means of the splint.

CASE XVIII (Fig. 490).—A. S. a forty seven year-old male was afflicted with pseudo-arthritis of the upper third of the left ulna of fifteen year duration. A Stader splint as applied on June 30, 1942, the head of the radius removed and bony union achieved. A 2 inch osteoperoosteal graft was inserted. The deformity as corrected by means of the splint adjustment.

CASE XIX (Fig. 491).—C. S. forty seven year-old male presented marked deformity and malunion of a fracture of the left wrist. Two previous operative attempts at correction had been made. A modified Stader splint as applied July 7, 1942, and the distal end of the ulna excised and secured as bony end. The osteotomy of the distal end of the radius.



A

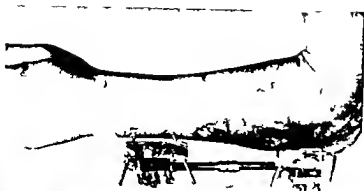


Fig 491 (Ca XIV C S) - M k d d f r m y d m l n f l f
 n s s f l p A M d f d S d p l p p l d B
 l p r s v f i l m C P p r a u y e w

Note The modified splint used in this case is applicable to minimally comminuted clavicle fractures requiring traction.

FRACTURES OF THE CLAVICLE

We present this case of comminuted fracture of the clavicle treated with the Stader splint only to show the splint's adaptability. At present we are not recommending its routine employment in clavicular fractures. This small splint is sufficiently rigid to maintain reduction of a clavicle fracture.



A



C

Fg 490 (Ca XVIII A S) - P d rth os f ppe hrd f l f
 ln f fif years dura A Stad d pl ppl d B P
 pera ra film C Post pera ra w



A



Fg 491 (C N C S) - M l d d f mty d mal f l f
 t f l p A M d f i d S d pl t ppl d B
 P p r y film C P p y w

Not The modified splint used in this case is applicable to comminuted Colles fractures requiring transfixation

FRACTURES OF THE CLAVICLE

We present this case of comminuted fracture of the clavicle treated with the Stader splint only to show the splint's adaptability. At present we are not recommending its routine employment in clavicular fractures. This small splint is sufficiently rigid to maintain reduction of a clavicle fracture.



Fig 49 (Case XX D M) - Comm d fra ture f l f l l A
 S d red ct spl ppl d B X ray film k first post pera
 d

CASE VV (Fig 497)—D M a twenty one year old male suffered a comminuted fracture of the left clavicle. The Stader splint was applied June 28 1947 free mobility of the entire extremity was obtained without discomfort

FRACTURES OF THE MANDIBLE

Fractures of the mandible with edentulous proximal fragments present a special problem not only because it is so

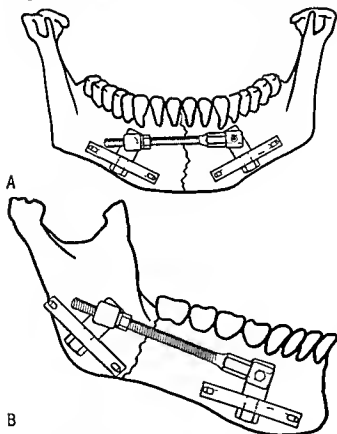


Fig 497—D grams of S d m d bl nts

W w l po t h th tr um f fracture f h m
 d l l by m f m l f sse f t f h pera
 f q l l l rth d be se l huma aim f trea g fract es
 f h m d bl sh ld be pe feet ocl

difficult to immobilize them by the usual methods of internal fixation but because they are so often compounded and associated with osteomyelitis. In many cases the fracture line extends through a remaining molar tooth which upon extraction causes the proximal fragment to become displaced upward and forward and outward. Converse and Waknitz recently have described a method of external fixation similar to

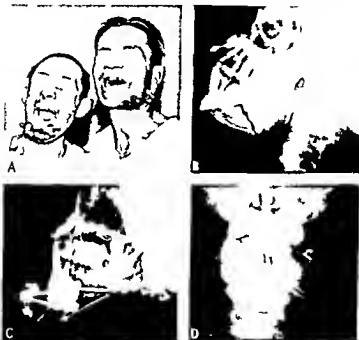


Fig. 494 (Case XVI J. H.)—Fracture of the mandible. A, frontal view of the patient; B, lateral view of the patient; C, postero-anterior (P.A.) radiograph of the mandible; D, lateral cephalometric radiograph of the mandible.

the type which we have been using. Six fractures of the mandible have been treated: three were fractures of the angle with edentulous proximal fragments in one of which osteomyelitis was a complication. The other three cases of multiple fractures of the mandible requiring multiple units and one instance of a fracture of the symphysis menti.

CASE XVI (Fig 494) — J H a fifty one year old male presented a fracture of the mandible with edentulous proximal fragment and osteomyelitis Extensive oral sepsis was present and



Fig 494 (Ca XVI T J) — Fracture of symphysis mandible with edentulous proximal fragment and osteomyelitis. Extensive oral sepsis was present and

most of the remaining teeth were loose. The Stader splint was applied on March 20, 1941, and removed on May 29, 1941. During this interval the patient had complete function of the mandible and was able to partake of solid foods. The osteomyelitis ran the usual course with sequestration and internal drainage which subsided before removal of the splint.

CASE XVII (Fig. 495).—T. J., a twenty-year-old male, suffered a fracture of the symphysis and angle of the mandible. This required the application of a multiple unit splint. The splint was applied on April 16, 1941, and removed on May 30, 1942. The residual malocclusion was corrected by subsequent rubber band splintage.

SUMMARY AND CONCLUSIONS

1. To date the Stader reduction splint has been employed by us in forty cases including twelve fractures of the tibia, three of the os calcis, two of the femur, five of the humerus, seven of the radius and ulna, one of the clavicle, six of the mandible, and two cases of transfixation of the hip joint, one of the knee joint, and one of the wrist joint. The results obtained were far more satisfactory than by any other method previously employed.

The application and adaptability of this splint to the treatment of various fractures, bone grafts, bone lengthening, and joint transfixation is not excelled or equaled by any other method.

3. The outstanding advantages of this splint are its structural strength and comparative light weight, and its mechanical design which permits complete control of bone fragments in all planes as well as traction, impaction, and fixation.

4. The method embodies the basic requirements of accurate reduction, rigid uninterrupted immobilization, immediate active motion, and early restoration of function in a single compact unit, eliminating the use of separate reduction frames, plaster, or weights and pulleys.

5. The above advantages render the splint the most ideal for use aboard ship, in field hospitals, and for the treatment of a large number of fracture casualties in the shortest period of time.

6 The postoperative care is reduced to a minimum joints are free for active motion and the danger of muscle atrophy is eliminated The unrestricted circulation and the active motion made possible by the splint favor earlier union

7 The insulation of the pins to prevent electrolysis about them thereby reducing pin seepage to a minimum is under study The findings thus far are very encouraging but not yet entirely conclusive

8 The Stader splint should be of considerable value to general practitioners who treat the majority of fractures

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THE RESULTS OF SULFONAMIDE PROPHYLAXIS IN THE SURGERY OF THE LARGE BOWEL

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d
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THE value of sulfonamides in the prevention of infection resulting from surgical operations on the large bowel has become increasingly well established as experience has accumulated. Before the advent of sulfonamides in no group of uninfected patients had fatal peritonitis been so frequent as in patients undergoing resections of the large bowel. Even following the less radical procedures on the colon such as colostomy serious intraperitoneal infection developed in a considerable percentage of patients.

Carlock and Seeley first reported the prophylactic use of sulfanilamide for resections of the large bowel. Their experience was distinctly favorable. In 1940 Lockwood and Ravdin reported a series of twenty-two operations on the large bowel and attributed the absence of peritonitis in this series to the prophylactic use of sulfanilamide. Since that time other sulfonamides have been given a trial. The drugs now available may be divided into two groups: (1) those which like sulfanilamide exert a general influence throughout all body tissues in favoring the resistance of the host by interfering

f S g l Se B H p l f h U rs ty f P syl
d h H so D p rtm f S g l R h Sch l f M d
U rs y f P
† H Prof ss f S rg ry d D ct f th H rnsso D p rtm
m f S rgical R h Sch l f M d U rs ty f P nsyl
N w L t Col l M d l Corp U d S es Army)
‡ A P fesso f S g l Rese h d Assoc S rg ry
School f M d Um rs ty f P syl A g D f th
H rnsso D p rtm f S rg l Rese h Uni rs ty f P nsyl
l A soc S g ry d S rgical Rese rch School f M d U
rs y f P syl

with the nutrition of invasive bacteria and (?) those whose action is largely confined to the gastro-intestinal tract and whose use is intended to lower the bacterial count of the feces

Second Group: General Effect through Body Tissue

In the first group are sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine. Among these *sulfadiazine* appears to have the broadest range of activity when administered systemically. However, recent experiments indicate that it as well as the other derivatives are inferior to *sulfanilamide* for intraperitoneal use. From the standpoint of toxicity it would seem that sulfanilamide produces a relatively high morbidity but a low mortality. Sulfadiazine creates less mental depression in our experience and results in a lower morbidity. However, its tendency to precipitate in the urinary tract occasionally leads to very serious degrees of oliguria.

Second Group: Act Locally on the Intestine

The drugs of the second group have failed to achieve the objective originally set up, namely, sterilization of the large bowel, but are nevertheless gaining a position of usefulness. Animal experiments originally led investigators to hope that *sulfaguanidine* would actually sterilize the feces in man. However, this did not occur. In their original report Firor and Poth obtained a count of coliform bacteria as low as 10,000 per cubic centimeter of feces. In this clinic we have never obtained levels lower than this. Furthermore, *sulfaguanidine* is absorbed to some extent into the blood stream and although it seldom attains a high blood level, toxic reactions have been relatively frequent. These may consist in drug fever and also in skin rashes.

A newer compound, *succinyl sulfathiazole*, is now the subject of clinical investigation. It appears to have definite advantages over *sulfaguanidine* and quite consistently brings about a marked reduction in the numbers of coliform and anaerobic bacilli. However, it does not sterilize the feces and therefore while it may become a useful adjunct in certain types of cases, its low antilacterial action in peritoneal fluid appears to indicate the concomitant use of another sulfonamide.

amide to check the growth of bacteria which gain access to the free peritoneal cavity. Succinyl sulfathiazole therapy alters the consistency of the stools encourages emptying of the bowel unless obstruction is severe and according to Poth may be employed as a substitute for other methods of preoperative bowel preparation. This may prove to be the most significant feature in the action of succinyl sulfathiazole.

The Drug of Choice

Experience to date so strongly supports the effectiveness of *sulfanilamide* itself in giving the necessary protection against spreading infection of the contaminated peritoneum that it has remained the drug of choice on our Service among agents whose use is intended to increase the effectiveness of peritoneal defense. Since *sulfanilamide* has yielded such satisfactory results in our hands we have hesitated to institute the regular use of a newer drug such as *sulfadiazine* which is unquestionably effective but capable of producing kidney injury in patients who are critically ill. Further experience may serve to justify an increase in the use of *sulfadiazine*. For local use *sulfanilamide* combines the virtues of high solubility and minimal tissue injury. We therefore favor using *sulfanilamide* whenever a locally applied drug is desirable not only in the peritoneal cavity but in other contaminated wounds as well.

DOSEAGE AND ADMINISTRATION

Sulfanilamide may be given either by mouth hypodermically or by slow intravenous infusion. It may also be applied locally at the operative site before the abdomen is closed. Since January 1, 1940 the average preoperative dose of *sulfanilamide* for patients undergoing resections of the large bowel was 3.6 gm. (or 5.5 gm. of *sulfadiazine*) the average amount of *sulfanilamide* used for local application at the time of operation was 6.8 gm. the average amount given subcutaneously after operation was 12.3 gm. and the average total amount of *sulfanilamide* given postoperatively was 16 gm. This last average excludes the use of *sulfonamide* drugs late in the postoperative period when they were sometimes used in

the treatment of urinary tract or respiratory tract complications. In calculating these averages we have excluded those patients who received no sulfonamide.

The present technique in use on the service of the senior author at the Hospital of the University of Pennsylvania is to administer 3 to 4 gm orally during the twenty four hours prior to operation. Four to 6 gm are then implanted locally and the administration of the drug resumed twelve to twenty four hours postoperatively in a dosage of 1 gm every six hours. This is usually given hypodermically at first but may be given orally if the patient is receiving fluids by mouth. If the patient is making satisfactory progress at the end of the third postoperative day the drug is usually stopped. Sometimes the dosage is reduced earlier than this if cyanosis or mental depression is marked. If any of the more serious signs of toxicity appear such as jaundice the drug is stopped at once.

TYPES OF OPERATIONS WITH RESULTS OF SULFONAMIDE PROPHYLAXIS

During the period between 1938 and 1941 fifty nine procedures were carried out on the large bowel in which the peritoneal cavity was opened and either a resection or an anastomosis performed. The operative mortality computed on the basis that all deaths in the hospital within thirty days of operation are operative deaths was 3.4 per cent (two deaths). The incidence of generalized peritonitis was zero. In this group of operative procedures resections were carried out forty six times with a mortality of 1 per cent (one death).

The tabulation gives a more detailed analysis of this series.

It is noteworthy that no attempt was made to do anastomosis by an aseptic technique. Every effort was made however to avoid gross contamination of the peritoneal cavity. For lesions of the right half of the colon ileotransverse colotomy was done with clamp. For lesion distal to this area the Rankin obstructive resection was utilized except when the position of the growth made this procedure impractical. For lesions too low in the sigmoid for this procedure yet distinctly above the pelvic floor the usual plan was to divide

the bowel distal to the lesion turn in the end of the distal segment and draw the proximal segment far enough out of the abdomen so that the tumor could be widely resected. Primary anastomosis of the colon was not practiced. Lesions in the rectosigmoid area were removed by combined abdominal-perineal resection. In a few of these cases preliminary decompression operations were performed but the abdominal and perineal portions of the resection were always carried out at one stage. It was the usual practice to repair the pelvic

TABULATION

OPERATION (S) RESECTION (R) ILEOSTOMY (I) (1938 to 1941)
(S) (R) (I) (S) (R) (I)

	S if m d T eat d	N Ch m th rapy
Right ileomyectomy	3	1
Left ileomyectomy	1	
Bloch-Mikulicz	1	
Mikulicz	3	
Mikulicz	4	2
Resection of sigmoid	13	1
Abdominal perineal	2	
Lockhart-Mummery	9	
Lockhart-Mummery	1	
Total	42	4
Ileostomy	12	1
Total	54	5

peritoneum with two separate and complete layers of sutures since during the early phases of healing this membrane alone protects the peritoneal cavity from the perineal wound.

In spite of the absence of peritonitis in this series it has not been our experience that sulfonamide prophylaxis eliminates wound complications. While it is the impression of the authors that wound infection has been less frequent and less virulent than was formerly the case this complication still occurs.

SUMMARY AND CONCLUSIONS

In a series of fifty nine operations on the colon in which the free peritoneal cavity was opened sulfanilamide was used in fifty four. The mortality was per cent. There were no deaths due to peritonitis.

The dosage selected on the basis of this experience for the average large bowel resection is 4 gm during the twenty four hours before operation 4 to 6 gm intraperitoneally and 10 to 12 gm in three days starting the day after operation. This dosage may be increased if the risk of peritonitis has been augmented by spilling large bowel contents in the peritoneum and it must be decreased if any of the toxic effects of sulfanilamide appear other than the customary cyanosis. The appearance of icterus during the administration of sulfonamides is regarded as sufficient reason to stop the drug.

Although peritonitis formerly was the complication of large bowel surgery most to be feared it has become an infrequent occurrence in this clinic since the introduction of the prophylactic use of sulfanilamide.

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- 12 P th E J K otts F L Le J T d I F B t ri P pe
 t f S lfa I m d a d Som f Its D es I S c yl lfa
 th l A N w Chem th p t Ag nt L c lly A t n th
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- 13 P th E J d K F L Cl cal U f S nylsulf h l
 A h S g 44 08 1942

CHEMOTHERAPY OF POSTOPERATIVE COMPLICATIONS

HARRISON F FLIPPIN MD FACPT

THE average surgical patient will usually pass through an uneventful convalescence if proper measures are employed before and after operation. Despite these precautionary measures however unavoidable postoperative complications do occur and require prompt and specific attention. The introduction of sulfanilamide and its related compounds into the field of chemotherapy has provided the surgeon with an efficient weapon which if properly employed will in many instances reduce postoperative morbidity and mortality. Since the fundamental concern of this clinic is with the use of the sulfonamides in the treatment of certain postoperative complications namely septicemia pulmonary and urinary tract infections the matter of other forms of therapy can receive no more than passing mention. *It is to be remembered however that regardless of the proved value of sulfonamide therapy it is not to be employed to the exclusion or neglect of other established therapeutic measures.* Only those drugs which have been accepted as being effective in the control of the above postoperative disturbances will be considered in this discussion.

GENERAL PRINCIPLES OF SULFONAMIDE THERAPY

To obtain maximum success with the sulfonamides in the control of the postoperative infections it is necessary to have an understanding of certain principles inherent in this type of chemotherapy. Since no two cases are identical in all their detail the following discussion of some of the impor

F m h l h l d lph Gen rat Hosp l d h School f At d
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f A soc M d School f M d U rs ty f Pen v l
As Ph Ph t l lph C rat Hosp l

tant problems concerned with their rational use may be applied to the several types of infections under consideration.

Mode of Action—Some appreciation of the mode of action of these compounds is more than a matter of academic interest as it is important to understand the factors which make for success or failure in the treatment of different types of lesions. Although the precise mechanism through which the sulfonamides exert their action is not completely defined we do have as a result of laboratory studies and clinical trial with these drugs some understanding as to the nature of the phenomenon. Reduced to simple terms the most plausible explanation of their action is as follows. Bacteria must have proper nutriment in order to multiply and apparently at some stage of bacterial reproduction a nutritive factor similar in basic chemical structure to the sulfonamides is required. This nutritive factor has been shown¹ to be para aminobenzoic acid although other substances may well play similar roles. Therefore should the bacteria be unable to distinguish between para aminobenzoic acid which is essential and the sulfonamides which have no nutritive value they cease to multiply and finally meet destruction.

Thus it appears that the sulfonamides possess a bacteriostatic effect which does not directly destroy the bacterial cells but which leads indirectly to the destruction of the organism by virtue of their antagonistic action through interference with bacterial proliferation. Hence the effectiveness of the sulfonamides against bacteria depends to a large extent on the ratio of the number of molecules of sulfonamide on the one hand and the bacterial supply of nutrient substance on the other. It is not surprising therefore that the antibacterial effect of these drugs is less in lesions containing large amounts of food for bacteria as is the case when necrotic tissue or pus formation is present. In such instances the sulfonamides are not to be employed as substitutes for surgical procedures but may be used in hopes of preventing a spread of the infection. The early diagnosis of pus containing lesions is of great importance not only as an aid in treatment but also the incidence of severe drug reactions is greater in patients receiving chemotherapy over long periods of time.

PHARMACOLOGY

The intelligent use of these drugs demands some understanding of the factors concerned with their absorption by distribution in and excretion from the body

Absorption—Sulfanilamide sulfapyridine sulfathiazole and sulfadiazine are sparingly soluble in water yet are well absorbed and attain greater solubility in body fluids. The drug concentration reached in the blood is dependent both on the rate of entry into and the rate of exit from the blood stream. Obviously when they are administered parenterally high blood levels are obtained more rapidly than when the drugs are given by mouth. In general absorption of these drugs is chiefly from the upper part of the small intestine with little if any taken up from the stomach. We may assume for practical purposes that they are all nearly completely absorbed from the intestinal tract into the blood stream within two to four hours after the ingestion of moderate (3 gm.) doses. After the fourth to sixth hour the amount of drug in the blood begins to diminish and if the blood concentration of the drug is to be maintained or increased it is necessary to administer additional drug in smaller amounts every four to six hours until the total dosage has been given. Since varying blood levels of these drugs result in diminished therapeutic effectiveness it is important to adhere to this schedule of dosage. The same principles of dosage apply when the drugs are employed parenterally although the time interval varies as to the route of administration and the drug selected.

Distribution in the Body—Following their absorption into the blood stream the sulfanamides are partially conjugated by the liver into the para acetyl derivatives which are less soluble less active and tend to be more toxic than the parent compounds. Approximately 30 per cent of sulfanilamide 30 per cent of sulfathiazole and 15 per cent of sulfadiazine appear in the circulating blood as acetylated compounds. Because of the irregular conjugation of sulfapyridine—10 to 90 per cent—it is impossible to predict the amount of acetylsulfapyridine present although the average is about 30 per cent of the total drug. Thus the usefulness of sulfapyridine has

been limited because of its irregular and at times high degree of acetylation.

The sulfonamides diffuse readily into the various body tissues and fluids after they pass into the blood stream. The tissue concentration however varies in relation to their vascularity so that diffusion into areas of chronic infection, bone and necrotic tissue may be deficient. The drugs are present in exudates and transudates in concentrations equal to or higher than those found in the blood. With the exception of sulfathiazole they pass readily into the cerebrospinal fluid in concentrations averaging 50 to 65 per cent of that present in the circulating blood. Because of the relatively low concentration of sulfathiazole attained in the cerebrospinal fluids—about 20 per cent of the blood level—its use in meningeal infections has been limited. The low concentration of sulfathiazole in the spinal fluid is not necessarily of great consequence because it is the existence of antibacterial concentrations of drug in submeningeal tissues curtailing bacterial invasion which probably limits the spread of the process as much as the drug in the spinal fluid itself. It is nevertheless desirable to have a bacteriostatic concentration of drug in the spinal fluid and for this reason sulfathiazole is not recommended for the treatment of meningeal infections although good results have been obtained with its use in certain types of meningitis.

Excretion—The sulfonamides both the free and acetylated forms regardless of the route of administration are excreted mostly in the urine and with the exception of sulfadiazine excretion of a single dose is almost complete within twenty-four hours. Only small quantities are found in the tears, breast milk, sweat, saliva or stools. The excretion of these drugs by the kidneys is reduced in the presence of renal damage and with a decrease in kidney function an increase in drug concentration in the blood occurs especially of the acetyl fraction. However the clearance of these compounds is definitely increased by an increased flow of urine and should the volume of urine become low the possibility of stone formation in the urinary tract by precipitation of crystals of the acetyl compounds except acetylsulfanilamide is greatly increased. Hence it is extremely important in order

to facilitate the excretion of the acetyl derivatives by the kidneys to maintain a urinary output of at least 1200 cc daily. This is best obtained by forcing fluids by mouth or if necessary parenterally. Because of the relatively high solubility of acetylsulfanilamide and its rapid excretion from the body we do not encounter kidney complications with sulfanilamide and the matter of urinary output is of less importance.

TOXICOLOGY

As is the case with many other chemotherapeutic agents the sulfonamides give rise to a variety of toxic manifestations and in order to employ these drugs intelligently one must be familiar with the potential dangers associated with their use. Fortunately most of these toxic effects are not serious and if the patients are closely followed the more severe reactions may be minimized. Furthermore the incidence of severe toxicity is increased with their prolonged administration but since these compounds exert their maximum therapeutic effect within a comparatively short period of time the necessity of continuing chemotherapy for longer than ten days is most unusual except in certain types of infections.

In order to recognize and control these toxic reactions the employment of certain clinical and laboratory procedures is essential. *Skin rashes* may occur at any time after the beginning of treatment especially after the fifth day. In such cases it is best to stop chemotherapy particularly if exfoliative dermatitis is present although the drug may be continued with caution if necessary. *Drug fever* is most commonly seen five to ten days after treatment has been started but may occur at any time. Not infrequently it is difficult to determine whether the temperature rise represents a drug reaction or a recrudescence of the infection. Except in complicated cases the fever if the original infection is usually normal by the third day of treatment and if the patient is clinically improved one should suspect a secondary rise in temperature as being due to the drug. Drug fever is often followed by dermatitis, hemolytic anemia or neutropenia and if it occurs treatment should be stopped unless the risk to the patient of continued infection seems greater than the risk of a severe

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drug reaction As a rule if the fever is due to the drug it will drop within twenty four to forty eight hours if the drug is discontinued and fluids forced

With the exception of sulfanilamide the toxic reactions involving the urinary tract constitute the most important problem in this type of chemotherapy. The renal complications are due in part if not entirely to the presence in the urinary tract of crystals composed of the drugs especially the acetyl portions. However the presence of crystalluria alone does not indicate renal involvement unless it is associated with progressive oliguria hematuria azotemia or loin pain. Not infrequently microscopic hematuria accompanies infectious diseases and unless a progressive number of red blood cells is detected or other evidence of renal damage is apparent cautious treatment may be continued but it should be remembered that hematuria is often a precursor of severe renal insufficiency. Obviously the appearance of gross hematuria or any of the above kidney complications is an indication for stopping the drug and at the same time fluids should be forced the urine alkalized and hypertonic glucose solution administered intravenously to promote diuresis. Occasionally ureteral catheterization is indicated but should be employed only after other measures have failed. Since crystalluria from these drugs appears to be less frequent in an alkaline urine it is advisable to administer alkalis in equal amounts to all patients receiving the sulfonamides except in certain urinary tract infections such as those due to the *Streptococcus faecalis* in which an acid urine affords better therapeutic results. However as mentioned above the maintenance of a urinary output of at least 1700 cc daily constitutes the most important factor in preventing the occurrence of severe renal complications.

Acute hemolytic anemia usually occurs during the first four days of treatment and requires cessation of chemotherapy and transfusion of citrated blood. Mild anemia of the hemolytic type is frequently seen and the drug may be continued but should the hemoglobin fall below 60 per cent transfusions are indicated. Depression of the white blood cells may occur at any time although there have been no cases of

agranulocytosis which developed within the first twelve days of treatment. It is best therefore to check the blood constituents every two to three days especially in cases requiring the drug for longer than ten days. *Nausea and vomiting* are the most frequent toxic reactions from these drugs and should the vomiting become severe it is advisable to check the serum chlorides.

CONTRAINDICATIONS TO SULFONAMIDE THERAPY

Theoretically the only possible contraindication to the use of the drugs is a history of a previous sensitivity to sulfanilamide or one of its derivatives. However in our experience there have been a number of instances in which patients have developed toxic reactions to one member of this group of drugs and not to another although this would not necessarily indicate that the patient would not have experienced an untoward reaction to the original drug. In such cases with histories of previous sulfonamide toxicity it has been our practice to administer chemotherapy at once and follow the patient very closely rather than withhold drug treatment. The presence of anemia, jaundice, acute nephritis, leukopenia or neutropenia per se does not contraindicate sulfonamide therapy as these conditions will usually disappear as the infection is brought under control by adequate chemotherapy. Obviously if such conditions are present necessary measures should be taken to detect their further development. We know of no medication or food which cannot be given to patients receiving these drugs.

SELECTION OF DRUG

The proper selection of drug to be employed in a given case depends largely on three factors. First from clinical trial with these drugs we have learned that certain bacteria are more sensitive than others to the various members of this group of compounds. It is important therefore to know which sulfonamide is likely to be most effective against the kind of bacteria involved. Second the drug must be one which is capable of being transported to the region of infec-

tion. Third, the drug selected should be the least toxic and at the same time satisfy the first two criteria of effectiveness. It is on the basis of these three factors that certain recommendations are made (Tabulation) but in view of the rapid

TABULATION

S E L E C T I O N		D R U G S	
<i>I n f e c t i o n</i>	<i>S e l e c t e d</i>	<i>D r u g</i>	<i>U s e</i>
Staphylococcus hemolyticus		Sulfadiazine	
Staphylococcus fecalis		Sulfathiazole	
Staphylococcus aureus		Sulfathiazole	
Escherichia coli		Sulfadiazine	
Bacillus pasteurii		Sulfathiazole	
Arobacter		Sulfadiazine	
Bacillus pyocyaneus		Sulfathiazole	
Streptococcus pyogenes		Sulfadiazine	
Pseudomonas		Sulfathiazole	
Meningococcus		Sulfadiazine	
Bacillus mallei		Sulfadiazine	

development of chemotherapeutic agents it is likely that some of the recommendations regarding the selection of drugs will soon be subject to change. Already reports have appeared indicating that sulfadiazine has replaced sulfapyridine and sulfathiazole in the treatment of many diseases and there is a growing belief among workers in this field that sulfadiazine will eventually supplant sulfanilamide.

ADMINISTRATION AND DOSAGE

Early Treatment

The best results with these drugs are obtained when they are administered early in the infection while the number of bacteria is still limited and the extent of tissue breakdown is at a minimum. Experience has shown that the length of time that elapses between the onset of an infection and the beginning of sulfonamide therapy represents the most important single controllable factor in the prognosis of the disease. Although it is important to make a bacteriological diagnosis in each case it is usually expedient to start chemotherapy on the basis of the clinical picture alone without waiting for the laboratory findings. This does not mean however that the necessary bacteriological studies are to be neglected as every

effort should be made to determine the causative agent. Not only is this of importance for the proper selection of drug to be employed but also in those cases where additional therapeutic measures are necessary such as the use of specific pneumococcic serum this knowledge is indispensable.

Methods of Administration

In general the *oral* administration of these drugs has proved to be the most satisfactory method in the treatment of acute infections. However in certain instances in which a rapid elevation of the blood level of the drug is desired or where oral medication is impracticable or impossible as after certain types of operations it is often necessary to resort to *parenteral* administration. Sulfanilamide because of its relatively high degree of solubility in water can be given subcutaneously or intravenously as an 0.8 per cent solution in sterile physiological saline. Best results with sulfanilamide parenterally are obtained with the subcutaneous route. In order to administer sulfapyridine, sulfathiazole or sulfadiazine parenterally it is necessary because of their physical properties to employ the sodium salts of these drugs. For intravenous therapy with these compounds a 5 per cent solution of the sodium salt in sterile distilled water is employed. Because of the slower excretion of sulfadiazine its use parenterally has given more satisfactory results than has sodium sulfapyridine or sodium sulfathiazole.

Dosage

Theoretically all patients treated with the sulfonamides should be followed by frequent estimation of the concentration of the drug in the blood. However experience with these drugs with the exception of sulfanilamide has failed to show any consistent correlation between therapeutic effectiveness and the blood level of free drug. Moreover certain factors such as kidney function, drug absorption and the state of dehydration all tend to influence the amount of drug found in the blood. Furthermore in many instances in which these drugs are used facilities for determining their concentration in blood will be lacking. Therefore it seems reasonable for

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TABULATION

Infected to	SELECT	Dose	Dose / Lbs
Streptococcus hemolytic		Sulfanilamide	S if d
Staphylococcus fecal		If thiazol	S if d
Staphylococcus		S If th azol	Sulf d .n
Cocci		S If thiazol	Sulf d az
Escherichia coli		S If th azol	S If d az
Bacillus proteus		S If th azol	Sulf d az
Neisseria meningitidis		S If thiazol	S If d
Staphylococcus aureus		S If thiazol	Sulf d
Neisseria meningitidis		S If d az	
Bacillus coli		If d az	
		Sulf d az	
		S If d az	

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ADMINISTRATION AND DOSAGE

Early Treatment

The best results with these drugs are obtained when they are administered early in the infection while the number of bacteria is still limited and the extent of tissue breakdown is at a minimum. Experience has shown that the length of time that elapses between the onset of an infection and the beginning of sulfonamide therapy represents the most important single controllable factor in the prognosis of the disease. Although it is important to make a bacteriological diagnosis in each case it is usually expedient to start chemotherapy on the basis of the clinical picture alone without waiting for the laboratory findings. This does not mean however that the necessary bacteriological studies are to be neglected as every

fection by proper surgical procedures to prevent reinfection of the blood stream

2 Sterilization of the Blood Stream—The most common organisms producing septicemias are the *Streptococcus hemolyticus* *Streptococcus viridans* *Staphylococcus aureus* *Escherichia coli* *Bacillus pyocyaneus* *Bacillus mucosus capsulatus* *meningococcus* *pneumococcus* and *gonococcus*. A number of bactericidal compounds have been used intravenously in an attempt to sterilize the blood stream but none of these agents has proved to be of consistent value. It is now generally recognized however that sulfanilamide and its related compounds are capable of destroying many types of bacterial infection in the circulation by virtue of their bacteriostatic action. According to the factors governing the selection of one of these drugs for the control of a given type of infection it appears that three of these compounds are of proved clinical worth for the treatment of septicemia. Sulfanilamide is the best drug for infections produced by the beta hemolytic streptococcus although excellent results have been obtained with sulfadiazine. Certainly sulfanilamide is the drug of choice in those cases with evidence of renal damage. Infections due to the *Staphylococcus aureus* *gonococcus* *Escherichia coli* and *Bacillus pyocyaneus* are best treated with sulfathiazole or sulfadiazine. Sulfadiazine is the best drug for infections produced by the *Streptococcus viridans* *pneumococcus* *meningococcus* and *Bacillus mucosus capsulatus*. Furthermore sulfadiazine because of its widespread action is the drug of choice in septicemia of unknown cause.

Dosage—In case of septicemia it is best to obtain concentrations of free drug in the blood of 12 to 20 mg. per 100 cc. In using sulfanilamide the desired concentration of drug in the blood can usually be obtained and maintained by an initial oral dose of 4 to 5 gm. followed by doses of 1 to 1.3 gm. every four hours day and night until convalescence is established. The above dose schedule applies also to the subcutaneous administration of sulfanilamide in an 0.8 per cent solution by the subcutaneous route although the rate of absorption by the tissues will influence the number of injections necessary. When sulfathiazole or sulfadiazine is employed

practical purposes to administer the approximate amount of drug which experience indicates will probably be therapeutically effective.

In discussing the dosage of these drugs it is well to point out several factors which influence the amount of drug that is necessary to obtain the desired results. The type of infecting organism must be considered both as to its susceptibility to the drug and as to the severity and type of lesion which it produces. Acute conditions involving soft tissues require different dosages than do urinary tract infections. It becomes apparent therefore that it is impossible to outline a course of sulfonamide therapy which will suit the needs of every patient. However once drug treatment has been started it is important to continue the drug until the patient has developed sufficient immunity against the infection to prevent a relapse. However the time required for the development of an immunity varies with individual patients and infections. A safe procedure to follow when in doubt is to reduce the dose gradually over a period of days and watch the patient carefully for any evidence of recurrent infection. Not infrequently a fall in temperature proves deceptive and a spread or recurrence in the infection will occur if treatment is stopped too early, or the infectious process will be masked by the action of these drugs and after chemotherapy has been discontinued the signs and symptoms of the infection will manifest themselves.

SEPTICEMIA

By septicemia we mean a generalized infection in which pathogenic bacteria multiply in and are carried by the blood stream producing definite symptoms and lesions. The disease may develop in any surgical patient with a pyogenic focus of infection that is insufficiently drained. The treatment of septicemia consists of (1) surgical removal or drainage of primary focus (2) sterilization of the blood stream and (3) general supportive measures.

1 Surgical Removal or Drainage of Primary Focus—The most important single factor in the treatment of septicemia is the location and removal or drainage of the focus of in

fection by proper surgical procedures to prevent reinfection of the blood stream

2 Sterilization of the Blood Stream—The most common organisms producing septicemias are the *Streptococcus hemolyticus* *Streptococcus viridans* *Staphylococcus aureus* *Escherichia coli* *Bacillus pyocyaneus* *Bacillus mucosus capsulatus* *meningococcus* *pneumococcus* and *gonococcus*. A number of bactericidal compounds have been used intravenously in an attempt to sterilize the blood stream but none of these agents has proved to be of consistent value. It is now generally recognized however that sulfanilamide and its related compounds are capable of destroying many types of bacterial infection in the circulation⁸ by virtue of their bacteriostatic action. According to the factors governing the selection of one of these drugs for the control of a given type of infection it appears that three of these compounds are of proved clinical worth for the treatment of septicemia. Sulfanilamide is the best drug for infections produced by the beta hemolytic streptococcus although excellent results have been obtained with sulfadiazine. Certainly sulfanilamide is the drug of choice in those cases with evidence of renal damage. Infections due to the *Staphylococcus aureus* *gonococcus* *Escherichia coli* and *Bacillus pyocyaneus* are best treated with sulfathiazole or sulfadiazine. Sulfadiazine is the best drug for infections produced by the *Streptococcus viridans* *pneumococcus* *meningococcus* and *Bacillus mucosus capsulatus*. Furthermore sulfadiazine because of its widespread action is the drug of choice in septicemia of unknown cause.

Dosage—In case of septicemia it is best to obtain concentrations of free drug in the blood of 1 to 0 mg per 100 cc. In using sulfanilamide the desired concentration of drug in the blood can usually be obtained and maintained by an initial oral dose of 4 to 5 gm followed by doses of 1 to 1.3 gm every four hours day and night until convalescence is established. The above dose schedule applies also to the subcutaneous administration of sulfanilamide in an 0.8 per cent solution by the subcutaneous route although the rate of absorption by the tissues will influence the number of injections necessary. When sulfathiazole or sulfadiazine is employed

the usual dosage by mouth is 4 gm followed by 1 gm every four hours. As a rule in order to obtain the necessary concentrations in the blood which are desired it is necessary to administer the initial dose of drug by vein. In those cases in whom intravenous therapy is necessary throughout the course of treatment repeated 2 gm doses must be made at six to ten hour intervals. The above schedule of dosage should be continued for at least seven days and in most instances this will be sufficient although such factors as outlined previously will influence the total amount of drug necessary for complete cure.

3 General Supportive Measures—Following the surgical treatment of the primary focus and the institution of sulfonamide therapy it is imperative that the patient's general health be maintained. Close attention to and the employment of appropriate measures for the correction of any disturbances in body fluids, electrolytes, blood constituents or vitamins constitute important factors in the treatment of septicemia. Furthermore in cases failing to respond to chemotherapy or in those unable to tolerate the drug the use of other therapeutic agents such as specific serum is indicated. Because of the relative ineffectiveness of sulfonamide therapy in staphylococcal septicemia we believe that all such cases should receive antiserum in addition to the drug.

POSTOPERATIVE PULMONARY INFECTION

The cause of pulmonary infection which follows surgical operations has been the subject of much thought and experimentation. It seems that in most instances a combination of factors such as shock, atelectasis, embolism and the abolition of laryngeal and bronchial reflexes favors the growth and invasion of ever present pathogenic bacteria. Numerous clinical postoperative pulmonary disturbances have been differentiated some of which represent fairly clear entities while others combine with and merge into one another. True pneumococcal lobar pneumonia is uncommon as a postoperative pulmonary complication as most such disturbances are the result of other forms of infection such as bronchitis, pneumonia or atypical pneumonia. In general the treatment of these pul

monary infections consists of (1) adequate chemotherapy (2) management of complicating factors and (3) general supportive measures

1 Adequate Chemotherapy—Postoperative pulmonary infection can be caused by a variety of pathogenic bacteria. The organisms most frequently associated with this group of diseases are pneumococcus usually one of the higher types *Streptococcus hemolyticus* and *Staphylococcus aureus*. Mixed infection is common and frequently two or more organisms are concerned in the causation of the infectious process. Sulfadiazine because of its wide range of antibacterial action and its relative low toxicity is the drug of choice for the treatment of postoperative pulmonary infections.

Dosage—Although we have been unable to determine any definite correlation between the effectiveness of sulfadiazine and the concentration of free drug in the blood it appears that if a free blood level of 5 to 10 mg per 100 cc is maintained satisfactory results may be expected. In order to obtain and maintain this blood level an initial 3 to 4 gm dose of sulfadiazine is given orally and followed by 1 gm every six hours thereafter until the temperature has remained normal for forty eight hours and the patient shows clinical evidence of improvement. It is possible in most cases to adhere to this six hour dose schedule but occasionally when a higher blood level is desired the 1 gm dose is given at four hour intervals until the desired drug concentration in the blood is obtained. Frequently in seriously ill patients it is well to give the initial dose of drug (3 to 4 gm) by vein and at the same time start giving 1 gm doses every four to six hours by mouth. Patients who are unable to take the drug by mouth are given 5 gm of sodium sulfadiazine intravenously every ten to twelve hours until the total dosage has been administered. In general the total dosage of sulfadiazine is 10 to 30 gm depending on several factors such as the presence of bacteremia, the type of disease when treatment was started, spread of infection and complicating diseases.

Management of Complicating Factors—Since the presence of pneumonia prevents the sulfonamides from acting on bacteria with the same maximum effect which they exhibit

in diffuse nonsuppurating lesions it is important that such pulmonary complications as empyema and abscess be attacked surgically. This does not imply, however, that sulfadiazine should be withheld as it should be used in hopes of preventing a spread in the infection. Usually in cases of massive pleural effusion chemotherapy and thoracentesis will prove sufficient but if the effusion is thick and purulent surgical intervention is indicated. The same principle of therapy holds true for any possible focus of infection elsewhere in the body which may be acting as a source of reinfection to the lungs.

3 *General Supportive Measures*—The general management of postoperative pulmonary disturbances is essentially the same as for cases of septicemia although certain additional measures are of importance. All patients with pulmonary infection should receive sufficient fresh air measures to promote adequate bowel elimination and prompt relief of abdominal distention. Such measures as enemas, rectal tubes, local heat to the abdomen and the use of pituitrin like drugs are often necessary.

If the pulmonary infection is regarded as *primarily atelectatic* dependent upon the obstruction of the bronchus by secretion every effort should be directed towards removing the obstruction. Frequent changes in position and deep breathing are indicated. Collections of secretion in the trachea should be aspirated. The employment of 5 to 10 per cent carbon dioxide in oxygen and steam inhalations are at times effective. Postural drainage with the patient on the unaffected side if the operative wound permits is occasionally helpful but often taxing upon the patient. If these simple measures prove ineffective in a case with signs of bronchial obstruction the bronchoscopic removal of the bronchial plug often produces excellent results but this procedure should not be deferred too long. From clinical observations it would appear that most cases of postoperative pulmonary infection are the result of excessive bronchial obstruction thereby necessitating the frequent use of these procedures.

In cases in which the pulmonary infection is considered *primarily pneumonic* the patient is treated as a case of pneu-

monia¹ It is often difficult to distinguish between atelectasis and pneumonia however unless massive pulmonary collapse or a lobar consolidation is present In the latter instance the patient should have complete mental and physical rest The intelligent use of morphine constitutes one of our principal aids in the control of apprehension restlessness and pain in such cases Also the administration of oxygen in pneumonia patients is often helpful in the relief of cyanosis and dyspnea

URINARY TRACT INFECTION

Bacterial infection of the urinary tract may develop following almost any type of operation and constitutes a common postoperative complication Theoretically this group of infections may involve the bladder or the kidney but usually the infectious process is not confined to a single organ or to the upper or lower urinary tract This discussion will be limited therefore to certain basic therapeutic measures which are applicable to all types of urinary tract infection The treatment of postoperative urinary tract infection consists of (1) establishment of adequate urinary drainage (2) sterilization of the urinary tract (3) eradication of foci from which bacteria are available for continuous reinfection of the urinary tract and (4) general supportive measures

1 *Establishment of Adequate Drainage*—Of all predisposing causes of urinary tract infection that of obstruction is the most important and no treatment is adequate until maximum drainage has been provided The most common cause of postoperative urinary tract infection is an overdistended bladder which may develop as the result of a neurologic disturbance or as the result of mechanical obstruction such as prostatic hypertrophy or urethral stricture This condition is often referred to as catheter cystitis and it occurs more often because of a lack in the proper use of a catheter rather than as a result of poor technique Upper urinary tract obstruction due to ureteral stricture stone tumor or an extrinsic mass may also cause urinary stasis Every effort therefore should be made to eliminate any possible cause of urinary tract obstruction in order to produce an adequately draining urinary tract

in diffuse nonsuppurating lesions it is important that such pulmonary complications as empyema and abscess be attacked surgically. This does not imply, however, that sulfadiazine should be withheld as it should be used in hopes of preventing a spread in the infection. Usually in cases of massive pleural effusion chemotherapy and thoracentesis will prove sufficient but if the effusion is thick and purulent surgical intervention is indicated. The same principle of therapy holds true for any possible focus of infection elsewhere in the body which may be acting as a source of reinfection to the lungs.

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In cases in which the pulmonary infection is considered *primarily pneumonic* the patient is treated as a case of pneu-

patients are indicated. Local irrigations may be of considerable help. Also the use of other urinary antiseptics such as mandelic acid, merhenamine and neoarsphenamine following the acute stage of the infection is a valuable adjunct to treatment.

PROPHYLACTIC USE OF SULFONAMIDES

The usefulness of the sulfonamides as prophylactic agents is difficult to evaluate, as one cannot be certain that infection has or would have occurred. However, it seems reasonable that if these drugs are effective in the treatment of certain established infections, they might well be employed prophylactically in the prevention of such infections. Already there has appeared in the literature a number of reports which suggest that these drugs are of value in preventing infection following accidental or surgical insult to the body, such as burns, traumatic wounds, compound fractures, appendectomies, bowel resections, pulmonary lobectomies, nephrectomies and transurethral prostatic resections. In view of the frequency with which subacute bacterial endocarditis follows the extraction of septic teeth or the removal of infected tonsils, it has been our practice to give sulfadiazine to all patients who require or congenital heart disease in whom these operative procedures are contemplated. Patients with chronic pulmonary disturbances, such as bronchitis and bronchiectasis, often develop septic pulmonary infection after operation and in such cases it seems advisable to administer the drug as a preventive measure. Furthermore, it is well to give the drug in patients requiring catheterization and cystoscopic examination to prevent the development of infection.

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2 *Sterilization of the Urinary Tract*—It is now well established that sulfonamide therapy properly conducted is an effective form of treatment for many types of urinary tract infections. The most common organisms producing post-operative urinary infections are *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus hemolyticus*, *Streptococcus fecalis*, *Bacillus proteus* and *Bacillus pyocyaneus*. Sulfanilamide, sulfapyridine and sulfathiazole have been used quite extensively in the control of these infections and from available data it appears that sulfathiazole is the drug of choice. Sulfadiazine has not been used long enough to determine its exact place although it shows every indication of being equally effective as sulfathiazole in urinary tract infections.¹

Dosage—In general the doses of sulfathiazole and sulfadiazine to treat urinary infections have been lower than those used to treat other infections. For most types of infections involving the urinary tract treated with these drugs, urinary concentrations of 50 to 200 mg. per 100 cc. are usually sufficient to sterilize the urine and such levels can be maintained by administering 3 to 4 gm. daily in divided doses. In certain patients however especially those suffering with severe infection it is often necessary to obtain higher concentrations of the drug in the urine (100 to 400 mg. per 100 cc.) thus necessitating larger daily doses (5 to 6 gm.). As a rule it is necessary to continue the above schedule of dosage for at least five days. Failure to respond within this time generally connotes some complicating factor.² Relapses of infection in the urinary tract are not uncommon and are usually the result of inadequate dosage or the fact that the drug has been discontinued too soon.

3 *Elimination of Focus*—There is no doubt that many urinary tract infections are produced as a result of infection in other structures such as the skin, bones, intestines and the genital tract. The elimination of the primary source of the infecting organism to prevent constant reinfection of the urinary tract is therefore of great importance.

4 *General Supportive Measures*—In the treatment of patients with urinary tract infections rest, adequate diet and systemic measures such as outlined for the care of septicemia

THE USE OF SULFANILAMIDE IN THE MANAGEMENT OF SPREADING PERITONITIS OF APPENDICEAL ORIGIN

CALVIN M. SMYTH, J. MD, FACS

PRIOR to 1939 the mortality from peritonitis of appendiceal origin constituted a challenge and a reproach to surgery. The wide spread of the mortality figures from different clinics roughly all the way from 5 to 50 per cent was difficult to interpret. The conflicting opinions expressed by competent surgeons regarding such important matters as optimum time for operation, nature and extent of surgery, omission or institution of drainage, to mention a few, made evaluation of any method of management almost hopeless. With the introduction of the sulfonamide drugs into surgical therapy it naturally followed that these should be applied to the treatment of acute appendicitis.

According to a recent editorial in the *Journal of the American Medical Association* Dees was probably the first to use sulfanilamide intraperitoneally. In 1940 the routine intraperitoneal introduction of the drug was adopted at Roosevelt Hospital, New York, and in 104 consecutive cases of acute appendicitis operation was performed without a death. The mortality in the preceding five years (1934-1939) in similar cases had been 7 per cent. These figures are dramatic but in attempting to interpret them one should bear in mind that the problem is not actually that of acute appendicitis. Acute appendicitis if treated by operation before the condition has spread beyond the confine of the appendix should have no mortality. If peritonitis has taken place into preformed adhesions the mortality should be negligible in competent

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According to a recent editorial in the *Journal of the American Medical Association* Dees was probably the first to use sulfanilamide intraperitoneally. In 1940 the routine intraperitoneal introduction of the drug was adopted at Roosevelt Hospital, New York, and in 204 consecutive cases of acute appendicitis operation was performed without a death. The mortality in the preceding five years (1934-1939) in similar cases had been 7 per cent. These figures are dramatic but in attempting to interpret them one must bear in mind that the problem is not actually that of acute appendicitis. Acute appendicitis if treated by operation before the condition has spread beyond the confines of the appendix should have no mortality. If perforation has taken place into preformed adhesions the mortality should be negligible in competent

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hands. In abscess resulting from localization of the condition the mortality should be low. The real problem therefore reduces itself to that of free rupture into the peritoneal cavity with spreading peritonitis without attempt at any walling off process. In attempting an evaluation of any new form of treatment the critical test should be applied only to this group and not to the much larger group of cases of acute appendicitis in general.

In October 1938 Raydon Knox and this writer in a special report to the Philadelphia Academy of Surgery collected from their services in six hospitals 696 cases of acute appendicitis with free perforation and spreading peritonitis. No cases of localized abscess were included. In this group there were thirty nine deaths a mortality of 5.6 per cent. These cases were all treated in the same manner since all three surgeons had had similar training. The McBurney incision was used and the appendix was removed in every instance. Six of the deaths occurred in cases in which the wound was closed without drainage of which there were a total of nine. These figures are given in order that a fair comparison may be made with a similar but much smaller group of cases treated in the same manner in our clinic but with the addition of sulfanilamide therapy.

TABLATION

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hypodermoclysis but not all had the drug introduced into the peritoneal cavity. No patient in the entire group died. This series is of course too small to warrant broad conclusions. However every series is important as a part of the collected experience of many surgeons.

Ravdin, Rhoads and Lockwood in a series of 757 cases in which operation was done since the introduction of sulfonamide therapy reported a mortality of 0.4 per cent, a reduction over their previously reported mortality of 1.5 per cent.

METHOD OF ACTION

Sulfanilamide when deposited in the peritoneal cavity develops a rapid and high concentration locally. This concentration may be anywhere from 300 to 1000 mg. per cent depending upon the quantity of the drug introduced. These concentrations are maintained for from twenty-four to thirty-six hours and in some cases slightly longer. Absorption from the peritoneal cavity is rapid and blood levels of from 10 to 15 mg. per 100 cc. may be expected within a few hours. Such levels however are not maintained for much over twelve hours. The severity of the infection and the amount of pus present definitely influence the rate of absorption. The more severe the infection the slower the absorption. Lockwood has shown that this is due to the inhibiting action of peptones.

CHOICE OF DRUG

With the introduction of newer sulfonamide compounds it is to be expected that sulfathiazole, sulfapyridine and sulfadiazine would be tried as substitutes for sulfanilamide. Sulfathiazole has probably been used more than the others. The relative freedom from side effects with sulfathiazole led a number of surgeons to use this drug in preference to sulfanilamide. The fact remains however that sulfanilamide is more effective against the organism most frequently involved in peritonitis of appendiceal origin. These are the colon bacillus, the hemolytic and non-hemolytic streptococcus and less commonly the gall bacillus group. Furthermore sulfanilamide in the crystalline form is the most soluble and therefore the most available of the sulfonamide group. It is the only one

in its presently available form that is capable of penetrating fibrin. Sulfathiazole is less soluble and when mixed with blood (or fibrin) tends to form concretions which not only become ineffectual but remain as foreign bodies capable of doing damage. The microcrystals of sulfathiazole are more soluble than the powdered drug but nevertheless act against a smaller variety of organisms of significance in the condition under discussion. It is the considered opinion of this writer that crystalline sulfanilamide is without question the drug of choice for intraperitoneal application and also for subsequent administration by other routes.

SELECTION OF CASES

With sulfanilamide as with any new remedy there has undoubtedly been a tendency to use it where no actual indication existed. There would seem but scant justification for introducing the drug into the peritoneal cavity in every case of acute appendicitis. While it has been shown by Key and others that the local application of the sulfonamides does not appreciably interfere with wound healing or tend to cause adhesions, it is the experience of many surgeons that wound secretion and capillary oozing are definitely increased. This may cause an indirect delay in healing and a predisposition to secondary infection after the initial bacteriostatic action has ceased.

With regard to localized appendiceal abscess there is some question as to the necessity for or desirability of employing the drug. Certainly it is difficult to recognize the indication for more than the initial intraperitoneal dose even where closure without drainage (a procedure not recommended) is done. In the writer's personal experience when sulfanilamide is introduced into a localized abscess there may be slightly less temperature reaction in the first twenty-four hours, however drainage is somewhat prolonged as compared to those cases of abscess in which the drug is not employed.

In the cases of free perforation with spreading peritonitis sulfanilamide finds its greatest indication. This statement must not be applied to those cases in which the drug is given as a

prophylactic before colon surgery is distributed locally about intestinal anastomoses

TECHNIC OF ADMINISTRATION

In the earlier cases it was not my practice to distribute sulfanilamide in the peritoneal cavity but to give the entire amount either subcutaneously or in the later stages by mouth. My present practice is to place the initial dose in the peritoneal cavity and follow with the remainder by hypodermoclysis. At the time of operation every attempt is made to remove by aspiration and gentle sponging all of the pus and infectious material. This removes in a measure the inhibiting action of the peptones to which reference has been made. In the average adult patient 8 gm. of the crystalline drug is distributed as uniformly as possible. In some cases the amount is increased to 10 gm. If the wound is to be closed about the incision an additional 2 gm. is spread in the layers of the abdominal wall. While up to 20 gm. may probably be deposited with safety, the desirability of such large amounts is open to serious question and they are not recommended.

As previously stated the recommended dosage brings about a rapid and high local concentration of the drug. Absorption follows at a rate either slow or rapid depending upon the degree of infection.

In from eighteen to twenty-four hours but not earlier administration by hypodermoclysis is started. For this 8 gm. of the drug is dissolved in 1000 cc. of physiologic sodium chloride solution. Of this solution 50 cc. is given every six hours the needles remaining in place. On the second, third and fourth day this dose is repeated. On the fifth day the dose is reduced to 6 gm. and on the sixth day to 4 gm. In my earlier cases I was inclined to discontinue the drug too soon. But accumulated experience has led to the adoption of the rule that when sulfanilamide is given it should be continued in most instances for a week. Too early discontinuance is frequently followed by recurrence of fever and other symptoms. When these occur after the drug has been stopped resumption of its administration is not attended by success.

It is essential that crystalline sulfanilamide be used and that

the mixture be heated to 60° C until solution is complete. Otherwise the drug will be thrown out of solution. The solution must be made fresh daily and any of it turning yellow or becoming cloudy should be discarded.

Nausea and vomiting seldom occur during the subcutaneous administration of the drug. I have seen jaundice as a complication only once and in this patient it was of only one day's duration. Cyanosis and disorientation on the other hand are common but I regard these as of no special significance or cause for concern. It is always well to forewarn the patient's family regarding these matters. This will save the family much worry and the surgeon much annoyance in the form of telephone calls and the like.

Blood level determinations and blood counts are made daily for the first three days and every other day thereafter while the drug is being given. Anemia may be of sufficient degree to require transfusion but in my experience this is not the rule and the blood picture rapidly returns to normal when administration is stopped. In no case have I encountered evidence of local irritation, abscess formation or sloughing as a result of subcutaneous administration.

SUMMARY AND CONCLUSIONS

From an analysis of the collected experience of surgeons during the past three years it would appear that the use of sulfanilamide has resulted in a definite reduction in the mortality of perforated appendicitis with spreading peritonitis. This reduction has been most striking in those clinics which reported low mortality in the overall statistics of acute appendicitis.

As pointed out earlier in this article it is dangerous to give too much weight to total mortality figures in acute appendicitis. The proportion of cases with perforation to total cases varies tremendously in different clinics depending upon the type of general practitioners referring the cases to the clinic. Thus in a community having a large proportion of well trained doctors who recognize acute appendicitis as such and promptly refer their patients for surgery the number of cases with perforation in relation to total cases of acute appen-

dicitis will naturally be small. On the other hand, in a community where the population relies on the hospital for medical care to the almost complete exclusion of the private physician, there is a tendency to use home remedies (for example, laxatives) in the earliest stages of appendicitis, and it will follow that the number of instances of perforation in relation to the total will rise. Since it is in the group with perforation that the mortality will be found, it is obvious that total cases mean but little in the evaluation of any change in the plan of management.

My own experience, as well as that of Ravidin and Knox, indicates that the routine use of sulfanilamide has resulted in a lowering of mortality through the saving of the group of patients who formerly died in spite of everything else we were able to do for them. I have made no other changes in the postoperative treatment, nor have I in any way modified my policy of operation upon diagnosis, regardless of the stage of the disease, routine removal of the appendix in all cases of free perforation, and the routine institution of drainage. It is therefore reasonable to assume that sulfanilamide has been responsible for this reduction in mortality.

If a word of caution is permissible at this point, I would emphasize the fact that sulfanilamide in the management of peritonitis of appendiceal origin is not a method of treatment per se. It should always be regarded as an *adjunct* to, rather than a substitute for, good surgery. Everything that we did to and for patients with spreading peritonitis before the introduction of sulfanilamide we must continue to do. I do not believe, for example, that the indications for closure without drainage have been legitimately extended through the use of sulfanilamide, nor that the incidence of such long recognized postoperative complications as residual abscess, fecal fistula, and intestinal obstruction has been reduced.

In short, sulfanilamide has proved itself to be a valuable addition to the armamentarium of the good surgeon in the treatment of a lethal disease, but when used by the inexperienced or occasional operator who relies upon the drug to overcome the inadequacies of his performance, the results will be disappointing.

the mixture be heated to 60° C until solution is complete. Otherwise the drug will be thrown out of solution. The solution must be made fresh daily and any of it turning yellow or becoming cloudy should be discarded.

Nausea and vomiting seldom occur during the subcutaneous administration of the drug. I have seen jaundice as a complication only once and in this patient it was of only one day's duration. Cyanosis and disorientation on the other hand are common but I regard these as of no special significance or cause for concern. It is always well to forewarn the patient's family regarding these matters. This will save the family much worry and the surgeon much annoyance in the form of telephone calls and the like.

Blood level determinations and blood counts are made daily for the first three days and every other day thereafter while the drug is being given. Anemia may be of sufficient degree to require transfusion but in my experience this is not the rule and the blood picture rapidly returns to normal when administration is stopped. In no case have I encountered evidence of local irritation, abscess formation or sloughing as a result of subcutaneous administration.

SUMMARY AND CONCLUSIONS

From an analysis of the collected experience of surgeons during the past three years it would appear that the use of sulfanilamide has resulted in a definite reduction in the mortality of perforated appendicitis with spreading peritonitis. This reduction has been most striking in those clinics which reported low mortality in the overall statistics of acute appendicitis.

As pointed out earlier in this article it is dangerous to get too much weight to total mortality figures in acute appendicitis. The proportion of cases with perforation to total cases varies tremendously in different clinics depending upon the type of general practitioners referring the cases to the clinic. Thus in a community having a large proportion of well-trained doctors who recognize acute appendicitis as such and promptly refer their patients for surgery, the number of cases with perforation in relation to total cases of acute appen-

THE EFFECT OF SULFONAMIDES IN WOUND HEALING

HAROLD A ZINTEL M D †

THE widespread use of the sulfonamides in the treatment of surgical wounds and the prevention of infections in civil and military practice has led to much speculation as to the actual effect of these therapeutic agents upon the rate of wound healing. Comparatively recently sulfanilamide and related compounds have been proved to be definite aids to proper surgical technic in the treatment of the infected wound. Gratifying results from this type of therapy have led to the use of one or another of the sulfonamides as a prophylactic or preoperative measure even in cases where the risk of infection is remote. Although there are differences of opinion as to their influence upon the healing of noninfected wounds no uncertainty exists concerning their value in the promotion of healing of contaminated or infected wounds as attested by several papers published by various authors.

PARENTERAL OR LOCAL CHEMOTHERAPY

Wounds do heal in patients receiving parenteral or local chemotherapy (Taffel and Harvey, Key and Burford, and Weil, Whitacker and Rushridge). Serosanguineous effusions have been reported (Casberg and Speed) as the result of excessive amounts of drug implanted in wounds. Local application of an excessive amount of a sulfonamide results in a dead space which in the natural course of healing is filled with a serosanguineous fluid (Key). The dose of any sulfonamide for local application as recommended by the Sub

†Frc th H rso D p rtm f S rg I Resea h School of M d
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abdominal wall wounds did not materially affect the rate of wound healing or the tensile strength of the wounds. In their work guinea pigs, rats and dogs were the experimental animals.

Sulfonamides in Treatment of Compound Fractures—Jenson, Johnsrud and Nelson reported that thirty nine cases of compound fractures treated by careful debridement and local implantation of powdered sulfanilamide and then closed primarily all healed by primary intention. Campbell and Smith did not feel that sulfanilamide reduced the number of infections in a series of fifty four cases of compound fractures treated with sulfanilamide locally. Most of the authors of articles on sulfanilamide in compound fractures agree that the incidence of infection is decreased significantly when the drug is used in conjunction with proper surgical management.

Sulfonamides in Treatment of Wounds for Skin Grafting—According to Veal, Klepser and DeVito¹ preparation for skin grafting of granulating surfaces of wounds with sulfanilamide has been very gratifying. However these authorities suggest that sulfanilamide itself may have an inhibitory effect upon the vascularization of granulation tissue and the growth of new epithelium.

EFFECTS OF ORAL ADMINISTRATION OF SULFONAMIDES ON DEGREE AND RATE OF WOUND HEALING

Bricker and Graham, after experimenting on dogs, concluded that sulfanilamide administered orally inhibited wound healing. Taffel and Harvey, and Zintel, Freshwater, Hardy, Harris, Neer and Robinson reported no appreciable inhibition or retardation of wound healing in animals to which sulfanilamide and sulfadiazine had been administered orally. In the experiments of Bricker and Graham, sulfanilamide was given orally to dogs in doses of 1.5 gm twice a day. Their experiments covered only from the third to the seventh post-operative days and therefore did not include all of the normal phase of wound healing. In view of the differences of opinion that had been presented and in view of the apparently contradictory experimental evidence it seemed that the subject might well be investigated under different environmental conditions. Studies therefore have been made cover

committee on Surgical Infections of the National Research Council is the amount necessary for a light dusting of the wound surface. This amount should not exceed 1 gm of drug for each 10 square inches of wound surface. Parenterally administered solutions of sulfonamides do not cause serosanguinous collections.

Choice of Sulfonamide for Local Use—Tissue culture technique has been used in the study of the toxic effects of the sulfonamides (Jacoby, Medawar and Willmer). Sulfanilamide and sulfathiazole in high concentrations are mildly toxic to human tissue cells as judged by the suppression of growth of fibroblasts, macrophages and epithelial cells. However, their toxicity is so slight that it may be disregarded and it disappears as soon as concentrations of the drugs are decreased. Sulfadiazine and sulfapyridine even in supersaturated solutions apparently do not produce this toxicity. Mayo and Miller⁸ believe that a saturated solution of sulfanilamide in normal saline solution stimulates wound healing. Effectiveness of antibacterial action remains the principal basis for the choice of a particular sulfonamide or a combination of sulfonamides for local use. One exception to this statement is the use of sulfadiazine in closed wounds. Sulfadiazine crystals have been found to be definitely undesirable in closed wound in the experimental animals because wound healing is delayed. Lyons and Burbank, in their review of local sulfonamide therapy, suggest that probably the most practical agent for use in superficial wound will prove to be a mixture of sulfanilamide and sulfathiazole.

Prophylactic Use of Sulfonamides in Clean Operations—Key and Burford have reported on the prophylactic implantation of sulfanilamide and sulfathiazole in clean operations. They report no postoperative infections in 150 consecutive cases. The average amount of sulfanilamide used was 5 gm, although on occasion as high as 10 gm were used. Sulfathiazole was used in eighty-seven of their cases with no clinical evidence of delayed wound healing when the drug was used in small amounts.

Harbison and Key found that the local implantation of moderate amounts of sulfanilamide in the jejunum or

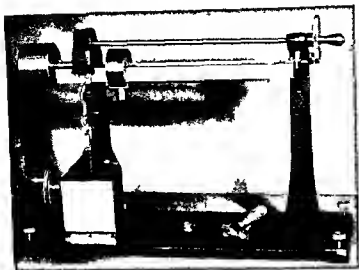


Fig 496—Tl t m

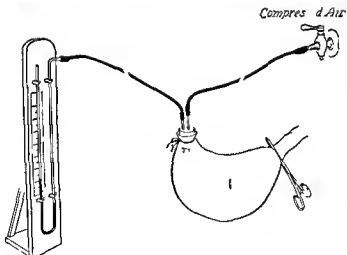


Fig 497—M f m f h g h f m h w d t v l m t
f p ess q d d rup h w d

mental incisions of the fascia and stomach. Silk sutures were used in the skin. Uniform blocks of skin and fascia measur

ing all of the phases of healing of several types of tissue in animals receiving sulfonamides by stomach tube

Experimental Study—The tensile strengths and histological reactions of skin fascia and stomach wall were used as criteria for the degree of wound healing. The experimental animal was the dog. Sulfanilamide and sulfadiazine, probably the two most widely used sulfonamides, were employed in these experiments.

The blood sulfonamide levels maintained were almost twice the average effective human blood levels. The sulfanilamide blood concentration averaged 19.7 mg per 100 cc, with a variation between 7.3 and 30.8 mg per 100 cc. The average sulfadiazine level was 17.7 mg with extremes of 6.7 and 36.4 mg. Administration of the drugs was by means of the stomach tube. Sulfanilamide was administered every eighth hour in 1 gm doses. Because sulfadiazine is both absorbed and excreted more slowly than sulfanilamide, it was administered less often, being given every twelve hours. One half gram of sulfadiazine per kilogram of body weight was administered as the initial dose; thereafter 0.25 gm per kilogram was given in each feeding. The sulfanilamide and sulfadiazine levels were determined at the end of the normal interval of feeding, i.e., at the end of twelve hours for the animals receiving sulfadiazine and at the end of eight hours for those receiving sulfanilamide. No doubt the true average blood levels during the experiments were higher than indicated by the figures given, because blood levels of sulfanilamide and sulfadiazine ordinarily begin to fall before the end of eight and twelve hour periods respectively. The drugs were given from the third day before operation until the time of sacrifice.

The animals were sacrificed at intervals from the third to the thirteenth postoperative day. Identical operative techniques were used on both control and experimental animals. Through a laparotomy, a 1 cm incision was made in the anterior surface of the stomach. Separate incisions were made in the anterior rectus sheath and in the skin. Thus the skin and fascia tested were not from the immediate vicinity of the laparotomy incision nor were the fascia and skin incision superimposed. Catgut sutures were used to close the peri-

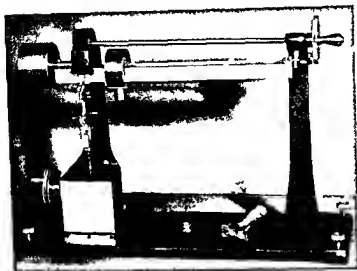


Fig. 497—Th m

Compre s d A r

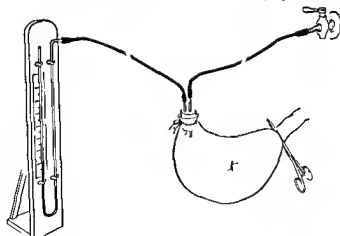


Fig. 497—M f m f th gth f m h w d by th m
f p s q d d rup th w d

mental incisions of the fascia and stomach. Silk sutures were used in the skin. Uniform blocks of skin and fascia measur

ing 1 cm at the line of incision were tested by means of the tensiometer (Fig 496) The strength of the stomach wounds

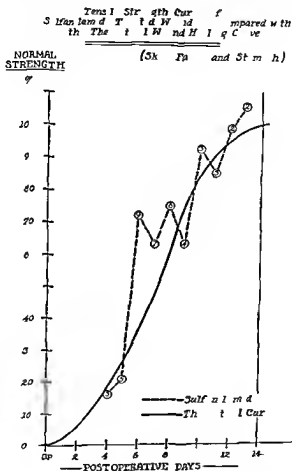


Fig 498

was measured by the amount of air pressure required to disrupt the wounds (Fig 497)

Results of Experiment—In Fig 498 are recorded the average tensile strengths of the wounds of the skin, fascia and

stomach of both the control animals and those receiving sulfanilamide. As the strengths of healed wounds of fascia, skin and stomach wall are not alike, they have been reduced to a

Tensile Strength of Control and Sulfanilamide Wounds Compared with the Tensile Strength of Healing Curve

(Skin and Stomach)

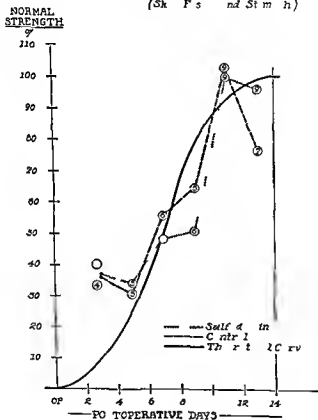


Fig 499

common denominator and expressed as per cent of normal strength.

Figure 499 is a graph of the tensile strength of wounds from

the third to the thirteenth days when adequate blood levels of sulfadiazine were maintained. The solid line represents the probable true strength increase of wound. This curve resembles the curve of many phenomena. It is very similar to the growth curve of yeast population, the growth curve of the fruit fly, and the curve of an autocatalyzed monomolecular chemical reaction as pointed out by Harvey in his studies on the growth of fibroblasts in the healing wound.

Although there are wide variations of some of the observations the general trend is very definite. Variations are observed in both the experimental and control animals and have been commented upon by other workers who have made similar studies (Harbison and Key).

Figure 500 presents photomicrographs of sections taken through the wounds of the stomach on the eleventh postoperative day. *A* illustrating the findings in a sulfadiazine treated animal and *B* in a control animal. Complete repair of the mucosa and union of the muscular layers by fibroplastic repair are well illustrated. Cellular repair is identical in both the control and the experimental wounds. Careful histological studies were made of all wounds. No essential differences in histologic repair were noted between the control animals and those treated with sulfanilamide and sulfadiazine.

Other factors known to influence wound healing were carefully observed. Hypoproteinemia and vitamin C deficiency have been demonstrated as retarding the rate of wound healing (Thompson, Rabin and Frank, Hartzell and Stone and Hunt). Serum protein levels were determined on each of the animals on the day of operation and at the time of sacrifice. Two animals had serum protein levels slightly below normal but these animals did not show significant changes from the general trend. Protein and vitamin C requirements were insured by a diet ample for all nutritional needs.

The healing of wounds of fascia, skin and stomach wall was not appreciably affected when more than adequate blood levels of sulfanilamide or sulfadiazine were maintained through all the phases of normal wound healing. The tensile strength of wounds of animals receiving sulfanilamide or sulfadiazine did not differ from the tensile strength of wound



f the control animals when tested at intervals between third and thirteenth postoperative days. Histologic sections failed to reveal significant differences in the degree of wo

healing between the control and experimental incisions. It seems reasonable to conclude therefore from these data and from clinical observations that adequate blood levels of sulfanilamide and sulfadiazine may be maintained for the prophylactic or therapeutic treatment of infection without inhibiting the rate of wound healing and without in any way jeopardizing the cosmetic result or the final strength of the wound.

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ONE STAGE ABDOMINOPERINEAL PROCTOSIGMOIDECTOMY

W WAYNE BABCOCK MD FACS†

d

HARRY E BACON MD FAPS†

CANCER of the abdominal and pelvic colon is a curable disease especially in the early stage when there is greater certainty that all malignant tissue may be located and removed. Occasionally even when there is evidence that the cancer has existed for one or two years recurrence does not take place during the patient's lifetime and in general the prognosis is better than that of a corresponding malignancy in any other internal organ.

Thus far *methods other than wide surgical excision have proved inadequate* to eliminate the disease. It should be borne in mind that approximately 80 per cent of all intestinal cancers are located in the sigmoid and rectum. In this area 60 per cent may be diagnosed by palpation while about 90 per cent are visible through the sigmoidoscope. Lesions above the mid sigmoid may be visualized roentgenographically with or without the double contrast method often before the development of subjective symptoms.

F m h D p rtm f S rg ry d P t l gy f mpl U rs ry
d th T mpl Un rs ty H p l
† P fess f S rgery d Cln l S g ry f mpl Un rs ty M d
cal Sch l Ch f f h S g cal Serv e Templ Un rs v Hosp al
Actn Co l S g ry Ph l d lph G ral Hosp tal
† P f ss d H d f th D parum t f Proct l gy Templ Un
rs ty M d cal School ll d f h D p rtm t f Proct logy St. M ry
H sp tal Co sul g P l gr R h D glas M cy d N nal
S m h H p tal

oped Particularly is it important that the diagnosis be made early in the 17 per cent of patients less than forty years of age who so often have a rapidly progressive type of malignancy



Fig 50 - M W g d fil l Ad m f rum
grad II Tl y d l f ll d by p m d
m l m p l d h g T d f tv rs f l m
l d l m Abd m p l p gm d
my Th y rs f p ph rs ct d p d q d

nan y The y ungest patients we have seen with carcinoma of the colon ere four and thirteen years old

C 1-1 r tl e ve rs a tv ent t v o v e a r o l d m e d c a l s t u d e n t
t l y i n g m l d n l u r g l l d e x p e r i e n c e d a l d o m i n a l c l e f t e r
h e m e l T h e f e e r e a t n g l e a r t l a t t h r e e c o n s e c

DIAGNOSIS OF MALIGNANCY OF THE LARGE INTESTINE

Early Symptoms

Unfortunately diagnosis has not kept pace with advances in the surgical management of malignancy of the large intestine. It is appalling indeed that many patients have very suggestive symptoms for months or even a year or more before seeking medical advice (Fig. 501). The public has not



FIG. 501—Mrs. D. d. s. ca. m. f. R. l.
 esm. d. h. rg. d. bl. d. g. f. w. l. d. gl.
 ou. l. d. p. th. Opera. p. l. p. m. h. vt. f. f.
 ral dra. p. ra. re. r.

become sufficiently aware of the ominous portent of recurrent abdominal cramp, pelvic tenesmus, and change in bowel habit toward constipation, or diarrhea in persons between fifteen and ninety years of age, or that blood and mucus in the stool frequently mean more than the presence of piles or fissure (Fig. 501). Mild abdominal colic, indigestion, particularly after a heavy meal, or flatulence are the common early symptoms of carcinoma of the transverse descending colon—often ignored or palliated until a sudden complete obstruction occurs or until the cachexia of inoperability has devel-

constipation is attributed to age. A patient recently seen had been given a year's supply of laxative so that she would not have to return to the doctor for that period (Fig. 503). Even the very significant *morning diarrhea* of cancer of the rectal ampulla may be treated as colitis for months. The *anemia* peculiar to carcinoma of the cecum not infrequently is studied and treated as an essential anemia (Fig. 504). The *melen*



Fig. 504—M. H. G. D. F. R. V. Y. R. S. A. M. F. R. V. Y. D. M. F. T. G. H. I. Q. I. N. Y. D. G. M. F. C. U. M. O. -S. T. G. I. L. A. D. I. P. -C. H. V. I. R. R.

is confused with the copious bleeding of internal hemorrhoids and endometritis (Fig. 505) which of course may be associated with malignancy. One patient reported two years treatment for piles without a rectal examination (Fig. 506). The *tenesmus* with the frequent small mucous dejecta of an anal cancer may be diagnosed as dysentery or proctitis or as a simple stricture and treated as in a recent case by division or incision.

tive tests on the Sunday afternoon on violent abdominal cramp distention and inability to move the bowels developed. He was attended by a physician for two days then referred to a surgeon who at operation found an intractable carcinoma and performed a pyloric resection. One month later the patient



Fig. 503. Mrs. M. G. D. (Mrs. G. D. D.) with advanced carcinoma of the face. The patient had been treated with various forms of therapy, including surgery, radiation, and chemotherapy, but the disease had progressed to this stage. The patient was found to have a large, ulcerated, and bleeding tumor on the right side of the face, which was the result of a carcinoma of the face. The patient was found to have a large, ulcerated, and bleeding tumor on the right side of the face, which was the result of a carcinoma of the face.

Although he was still healthy, muscular and appeared in good health, we found a far advanced carcinoma of the colon with metastasis.

But, and it is to be especially regretted, delay is more frequently due to the physician than to the patient. Often the physician fails to be alert to the early, milder symptoms. The

constipation is attributed to age. A patient recently seen had been given a year's supply of laxative so that she would not have to return to the doctor for that period (Fig 503). Even the very significant *morning diarrhea* of cancer of the rectal ampulla may be treated as colitis for months. The *anemia* peculiar to carcinoma of the cecum not infrequently is studied and treated as an essential anemia (Fig 504). The *melena*



Fig. 504—A. H. G. D. F. R. Y. R. S. A. M. F. T. W. Y. E. A. R. S. T. R. E.
P. D. G. D. H. I. M. T. G. H. P. U. D. I. S. M. F. R. T.
E. T. I. Q. D. A. J. D. E. O. S. M. F. C. U. M. O. S. T. G.
L. K. I. I. I. I. M. P. C. I. D. R. A. R. Y.

is confused with the copious bleeding of internal hemorrhoid and metritis (Fig 505) which of course may be associated with malignancy. One patient reported two years treatment for piles with out a rectal examination (Fig 506). The *ten sins* with the frequent small mucous dejecta of an anal cancer may be diagnosed as dysentery or proctitis or as a simple fracture and treated as in a recent case by division or incision.

tive tea on one Sunday afternoon violent abdominal distention and inability to move the bowels developed. He was attended by a physician for several days then referred to a surgeon who performed a laparotomy. At this time a carcinoma of the cecum was found. The patient died on the 15th day after operation.



F 501—Mrs M. d. r. w. r. f. ears. Ad. ca. m. f. rectum
Co. sup. f. f. ur. m. th. gn. last. powd. rs. last. ea.
Rectal discharge. f. m. cu. d. bl. d. f. k. O. bd. m.
p. ri. l. p. octo. om. d. my. P. d. d. em. d. mpl. l. b. m. d.
ff.

although he was still heavily muscled and appeared in good health, we found a firm nodule in the cecum. The patient died.

But and it is to be especially regretted delay is more frequently due to the physician than to the patient. Often the physician fails to be alert to the early malar symptoms. The



fg 500 - M C g d f tv rs C m f gm d
 Tl m l l m h m l p Al d m p cal
 p gr l so m d Sc l p x f d -
 f l l T l l



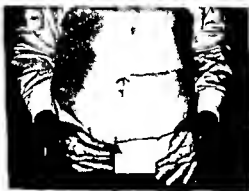
f g 0 - Mrs G g d ty ars Ca f h ctowgm d d
 gr l lymph O y ml T d f d m Sc l
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 Ca d d l p l d ra d d
 Abd mun p r r eal p oct om d m sgm d p ll d h gl pl
 S h f p m as d l em d f m pe m
 Good rung w h l g



Fig. 508—A. W. g d f ty y rs Ca m f pl fl
 W m l ra p l l d l d d ools f
 l s f s po d Fl d f pl fl Res ti f spl na
 fl xu d -e d h l mp-ch m dra D h rg d h
 h re l l f p re Co d ll w y rs ft pe
 t



Egg 507-VI L. g d f rs G m f tum Egl
 m h h g l l h l h h m h
 d x h h blood Abd m p l p om d m T r
 f p rs g d d d l p l pt l l l l



1 b 508-VI W g d f ty v Ca m f pl fl
 VI l 1 p f l d bl d d t l f
 loss f 5 p d Fl g d f a pl fl vt R tu f pl
 fl xu d -e d moc l l mp hm v dra D h g d th
 l rt l d y f p Co d ll tv y rs f p

Often the general practitioner suspects that a carcinoma may be present but, distrusting his own diagnostic ability, refers the patient for roentgenologic study, not realizing that *carcinomas of the pelvic colon are rarely delineated by x rays*



1 50' -Mrs. B. d. fifty-eigh. rs. Th. l. ear. f.
 tl. rs. l. Bl. ry. dra. ges. f. m. art. bd. m. al. l. d.
 p. f. ca. \ d. on. h. h. l. yst. Op.
 sub. l. l. m. d. o-e. d. as. moe. R. ry.

In about 10 per cent of patients we have seen with cancer of the bowel below the pelvic brim a negative or incorrect diagnosis had delayed the necessary operation for weeks or months (Fig. 502).

Diagnostic Considerations

For the early recognition of carcinoma of the abdominal colon x ray studies are of especial value. They may be compromised however by the lack of experience and thoroughness of the roentgenologist. Particularly may roentgen examination be misleading if the examiner depends upon the study of the films without manipulation of the colon under the fluoroscope. The *roentgen diagnosis* of an intestinal carcinoma that does not exist or absence of carcinoma when one may be demonstrated by expert examination is not rare and indicates the need of thorough training and careful scrutiny of all possible findings before reaching a conclusion. An error may be of little moment if it does not delay needed operation as illustrated in the case of a patient whose roentgen diagnosis was cancer of the sigmoid. The sigmoid proved to be uninvolved. The cancer readily diagnosed by the finger was in the lower rectum where it could not be seen on the film.

An occasional error is to give the *barium by mouth* when a lesion of the colon exists. The barium fills the small bowel obscures the lesion in the colon and may precipitate or intensify obstruction and even lead to rupture of the bowel. A barium enema is sometimes given after barium by mouth which does not clarify the problem or improve the patient's condition.

CASE II.—A man fifty-four years for several weeks had experienced abdominal cramps after eating but had been advised that many adults had such discomforts and that he should ignore them. After an attempt to eat a full course dinner symptoms of complete obstruction developed and a delirium was generally induced. He was finally filled with small intestine tubes of curing any definite present in the colon (Fig. 510). A second roentgenologist then saw the futility of barium enema and could offer no solution as to the preoperative location of the obstruction but remarked that the lesion was at the splenic flexure. On exploration a small growth of the right half of the transverse colon was found. On lifting the greatly distended proximal colon it burst and great abdominal cavity with great quantities of fecal material. It was evident that to cure the inflammation



tals immediately attach to the peritoneum. A rapid Mikulicz resection was done and three double lumen suction drains were inserted to various parts of the abdomen. The lower drain under constant motor suction evacuated fecal particles from the pelvis up to the seventh day.

More serious is an unnecessary operation due to faulty roentgen interpretation. There is a blind area in the lower sigmoid where at times carcinoma may not be felt by the finger reached by the proctoscope or in certain cases delineated by roentgen examination and where positive symptoms may rarely justify an exploratory operation.

In the diagnosis of *carcinoma of the pelvic and terminal portions of the colon* x ray has no place except to detect in visible or metastatic lesions of bone and lungs. In this location is a rule the primary growth is easily felt and diagnosed by the finger or seen through the proctoscope. When first seen about 98 per cent of these growths have developed unmistakable characteristics of malignancy and diagnoses made from the tactile impressions received by the trained examining finger are least subject to error. Why bother with an uncertain and undependable roentgen ray silhouette in searching for something that can be definitely felt or clearly seen through a proctoscope.

CASE III.—A man fifty had for five months a persistent diarrhea with frequent liquid stool containing blood. To eliminate the possibility of carcinoma roentgen study after a barium enema was advised and repeated negative for carcinoma. The doctor then studied bacteriologically and the patient treated for three months with sulfanilides and bacterial products. Unrelieved he then consulted a chiropractor who at once intro-

Fig 510—M	M	g d f r y f	r s A	l	carc	m	f tra
re	l	f	h	l d m	l d		
g f ll	g d	r y d	F		w k	ps	b pa
m	g f ll w	g ga	est	l l n m	X	d enos	b scu d t
t m Opera	tra	re	l ct	Bo	l b est fl	sl g h	t
d	w h t	m	l fecal	l Th	mp dra	h f w	
m	g fec l p rt	les f	h pel	p d	h d	R t	h t h
ca l	thre	r s f	pera				

duced a finger in the rectum and discovered a cancer a few inches above the anus.



Fig. 511—M. H. G. aged 55 years. History of chronic constipation, m. d. D. irritable, m. h. T. b. ps. m. h. p. rt, g. f. ea. ea. d. f. pd. Th. d. b. ps. d. ca. ma. g. d. H. M. k. l. pera. I. llen. d. n. tv. d. h. If years f. pera.

A central ulcer crater smooth or irregular with surrounding raised rolled often circinate or sinu u borders the edges of which may be ragged and irregular but have a characteristic firmness and infiltration that extend deeply into the wall of the bowel—fin lines present in about 98 per cent of

cancers of the rectum reached by digital examination—we consider absolutely dependable. There is no type of ulcer that mimics it. With a small infiltrating plaque which represents the very rarely seen initial lesion of cancer of the bowel and with polypoid growths especially those without umbilication and infiltration of the base a biopsy is necessary yet the biopsy may fail to sample the malignant stainable portion of the growth. A biopsy improperly taken or with the histologic appearance blurred by an inflammatory or degenerative process may lead one to mistake a carcinoma of the bowel for a benign process (Fig. 511). We can report a number of such errors and the person who selected the bit of tissue removed may be at fault rather than the pathologist.

Opportunity to Consider

The surgeon as well as the specialist or general practitioner may be responsible for a dangerous delay because he sometimes operates for a preoperative diagnostic finding rather than with an open exploring mind. He may overlook carcinoma of the colon in the curable stage unless he keenly evaluates the leading symptoms. With any suggested diagnosis of piles fissure fistula diverticulitis and rectal stricture carcinoma should first be excluded. For example in a patient now convalescent the colic was felt in the upper right abdominal quadrant because the proximal transverse colon was contracting against a partially obstructed descending colon. The surgeon accepted the diagnosis of gallbladder disease and finding little evidence of a cholecystitis at operation did an internal drainage of the gallbladder without relief. Some weeks later the family physician felt the hard malignant mass in the descending colon. In another case the surgeon refused to heed the family physician's suggestion that the upper rectum be examined carefully for cancer before he operated upon the obvious hemorrhoid. The distress of another patient was referred to the pelvis the sigmoid being in spasm from an annular growth near the rectosigmoid junction but as a bimanual examination showed an enlarged uterus a hysterectomy was done without investigating the pelvic colon. A fourth patient with pelvic distress from a rectal carcinoma

had the relaxation from childbirth corrected by a vaginal plastic operation. How helpful it would be if every human examination were made also through the rectum!

Partial or complete obstruction with its associate proximal intestinal colic rarely occurs from carcinoma of the right colon for the intestinal contents are liquid in this area and the growth is rarely of the annular constricting type so common in the left half of the colon. The mass and local discomfort may be interpreted as appendiceal and drainage operations have been done leading to chronic malignant sinuses and fistulas.

It is surprising that patients with evidence of only moderately advanced cancer of the bowel are occasionally advised that radical excision is of no avail and that irradiation, electrocoagulation and other totally inadequate local destructive measures be used (Fig. 505). Although we have mentioned a number of diagnostic errors as a stimulus to earlier and more accurate recognition of this very common and dangerous disease, it is evident that year by year malignancy of the large bowel is being diagnosed earlier and is receiving more radical treatment in higher percentages of patients with a resulting increase in the number of cures. With these marked general improvements there has been a decided lag in the elimination of unnecessarily mutilative procedures.

Colostomy was an important operation in the day when cancer of the bowel was considered irremovable. It remains incorporated as an essential part of the most popular operation performed upon the colon. The *anus and functional sphincter are sacrificed* although entirely free from the disease. We are beguiled by such sophistry as that colostomy is essential to prevent recurrence, that the peritonitis cannot otherwise be made radical and that at any rate by modern methods colostomy has been made not only bearable but comfortable, convenient and desirable. It is true that the old Kraske and similar perineal operations often left structured and retracted perineal openings that gave the patient much more annoyance than a well made abdominal colostomy. The memory of these unsatisfactory operations doubtless has largely colored the views of modern surgeons. It is not re-

alized that when a good abdominal colostomy is moved to a sphincterless perineum it becomes a better and much more convenient outlet (Fig 51) Then in the majority of cases



Fig 51 - Mrs B g l l rty v rs Ad m f g
d l g ru Ald l ramp ch h m l m h
T p l d l pera rp g l b d d b
ve f dl P ll loc m d Abd m pe l p oct
en d ct m h h ct d rs pl f l st m
pen N l g Rec l dea h f th rs

it n longer necc itates the c n t n t wearing of a pid or
other protecti n

The *sphincterless perineal colostomy* discharges less obvi

had the relaxation from childbirth corrected by a vaginal plastic operation. How helpful it would be if every human examination were made also through the rectum!

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ficient life expectancy we have made it a practice to remove the diseased segment of bowel without an abdominal colostomy even when it is impossible to remove all adjacent malignant or metastatic tissue. If metastases to the liver are small or limited in extent and the patient is in fair condition a resection of the primary growth without colostomy usually is worth while. The patient's health improves after the removal of the necrotic and infected ulcer, the abnormal discharge and loss of blood cease and the physical improvement is associated with much mental relief.

Colostomies performed for conditions other than carcinoma of the large bowel also have been removed as in lymphogranuloma with removal of the diseased rectum and transplantation of the sigmoid colostomy to the perineum, destruction of the rectum by roentgen ray and radium irradiation for carcinoma of the uterus, the remains of the rectum being removed and the sigmoid colostomy mobilized and brought through the anal sphincter, congenital absence of the lower rectum and anus, the pelvic colon entering the base of the bladder for which colostomy had been performed soon after birth. In this case it was necessary to disconnect the pelvic colon from the bladder, close the vesical fistula and transplant the pelvic colon to the perineum, the two colostomy openings were eliminated by end to end suture.

Occasionally after a palliative colostomy for an advanced cancer of slow evolution of the rectum or sigmoid it is possible to remove the diseased segment of bowel and eliminate the colostomy either with an end to end anastomosis or transfer of the sigmoid opening to the perineum. The patient is then relieved of the primary necrotic ulcerating growth with its often severe discharge and toxic obstruction and diarrheal symptoms may not recur. Mild irradiation may be used to retard the lymphatic extension of the disease. After such a resection, anastomosis and elimination of a palliative colostomy, one patient a physician appears and feels well and for several months has been able to operate and conduct his practice.

In recent years the lowest mortality rates from resection of the colon have been reported by surgeons who have become

ous amounts of offensive gas requires less frequent evacuative or other measures and in general is highly preferred to the abdominal colostomy. To many persons a colostomy is a serious handicap despite the improved methods of caring for intestinal elimination. The transfer to the perineum removes a bar to obtaining employment to the practice of a profession to social intercourse and to marriage. This is the testimony we have accumulated from eighteen patients on whom we have eliminated abdominal colostomies present from a few weeks to fourteen years.

TREATMENT

The ideal treatment of cancer of the colon and rectum is radical extirpation with restoration of the continuity of the bowel. No artificial anus can be as efficient nor can equal the comfort of the natural mechanism. Next in desirability is radical extirpation with a colostomy placed in the situation of the natural anus. The value of a method will be determined by several factors: (1) low mortality, (2) high rate of operability, (3) the experience of the surgeon, (4) completeness of excision and percentage of cures. A one stage procedure has many advantages and now may be made as radical as and can be done with a mortality that competes well with stage procedures.

Occasionally a *palliative colostomy* is done because the primary growth is considered inoperable or because there is evidence of metastasis in the liver or elsewhere. We believe that a palliative colostomy should rarely be done. If the growth is so extensive that the patient has only a few remaining weeks to live a colostomy adds a burden to all concerned with too little benefit to compensate for such an offensive annoyance. In such cases it is better to let the patient drift out while using a *nonresidue diet and adequate sedation*.

There is a considerable percentage of growths however in which a resection and anastomosis may be done. The patient relieved of the obstruction and without an abnormal abdominal opening may lead a nearly normal life for two years or more with relative comfort. He may even resume his previous occupation. In such cases provided there is a suf-

With infusion spinal anesthesia becomes the safest of all anesthetics for intestinal surgery. Lemmon's continuous spinal anesthesia has advantages for very prolonged operations but sometimes the needle will become obstructed or displaced from the dura in which case one should continue with pentothal sodium intravenously and local anesthesia rather than to turn to ether or gas. The inhalation anesthetic causes straining, gagging and vomiting which may force the intestines through the wound and seriously interfere with the operation.

C I c Resect

END TO END ANASTOMOSIS SINGLE STAGE ONE CLAMP METHOD (Fig. 513)—For resections of the colon above the pelvis our preference at the present time is for end to end anastomosis and complementary appendicostomy or enterostomy well proximal to the anastomosis. Following the development of nonirritating suction drains for the peritoneum (Fig. 514) a satisfactory one clamp method of end to end anastomosis and the use of fine alloy steel wire intestinal suture the mortality of the end to end anastomosis of all parts of the abdominal colon now compares favorably in our experience with the Paul Mikulicz exteriorization procedure while the morbidity is much less. The operation is possibly a little more dangerous in resection of the sigmoid and recto-sigmoid but surely it is safer for the right and transverse portions of the colon where a modified Mikulicz procedure has given a mortality of 10.6 per cent in expert hand. From 37 recent consecutive aseptic end to end anastomoses of the colon there were three deaths or a mortality of 9.4 per cent.

One patient, a man of seventy three years whose cecum was involved died suddenly from reaction to the intravenous infusion of glucose. Previously he had shown alarming symptoms during the glucose infusion. The second patient had renal suppression, hematuria and ileus without leakage or peritonitis. The third, very obese and with advanced cancer of the lower sigmoid had necrosis of the proximal segment with leakage. Several of the patients who recovered were more than seventy and one was eighty five years old. One had an associated resection of a cancerous stomach, transverse

adept in a single stage operation. We have found the single stage procedure of advantage even when it has been necessary to resect in addition a portion of infiltrated bladder abdominal wall the ureter stomach adjacent intestine vagina or to remove the uterus and appendages. In recent years it has not been found necessary to compromise one of these prolonged complicated single stage operations because of shock or other unfavorable condition and in our experience none of the resectable patients have failed to react from the extensive operation.

ABDOMINOPERINEAL PROCTOSIGMOIDECTOMY

For the acute and intense forms of obstruction where there is probability that virulent bacteria have already entered the peritoneal cavity preliminary decompression by cecostomy or appendicostomy should of course precede the radical operation.

ANESTHESIA

Spinal anesthesia is used employing 8 to 12 mg. pontocaine mixed with 8 to 12 mg. of procaine injected with barbotage through the first or second lumbar interspace. This gives a satisfactory anesthesia lasting from two to three and one half hours. The upper part of the body should be elevated during the first ten minutes of the anesthesia after which it is depressed. An associated local infiltration of the abdominal wall with 10 to 50 cc. of 1 per cent procaine solution containing 1 drop of 1:1000 epinephrine solution to each 10 cc. supplies a desirable fluid and stimulus.

Should the spinal anesthetic wear off before the completion of the operation small amounts of 5 per cent pentothal sodium sufficient to cause a light amnesia are given intravenously combined with local and splanchnic anesthesia produced by additional quantities of the procaine epinephrine solution.

The debilitated patient should have a needle in a vein with constant drip infusion of saline and 5 per cent glucose during the operation. This also provides a channel for the prompt administration of blood plasma and stimulants.

were formerly considered very hazardous but now we believe it possible to obtain a superior result by careful attention to detail especially with elderly debilitated patients who often do not well withstand prolonged confinement in bed and repeated operations

The *loop of cancerous colon is liberated* with attached peritoneal folds mesentery and lymphatics The arms of the loop wide of malignant tissue are aligned by two lateral guy sutures on each side and divided between Payr or short clamps by cautery This leaves the distal and proximal ends of the



Fig 514-Gl p g mp l et g b l d m p mp d
f t d mu l p

colon or ileum and colon crushed together in a single clamp which is turned over and two or three rows of seroserosal sutures introduced the outer row being of interrupted No 36 alloy steel wire sutures The clamp is then rotated back to its former position and a continuous Cushing suture of chromic catgut introduced anteriorly over the clamp As the clamp is partly opened and withdrawn this suture is tightened inverting and closing the anterior edges of the bowel without leakage One or two additional anterior outer rows of interrupted seroserosal sutures of No 36 alloy steel wire are inserted corresponding to those introduced on the posterior

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colon and intermediate abscess a second a combined end to end resection of a cancerous jejunum and transverse colon

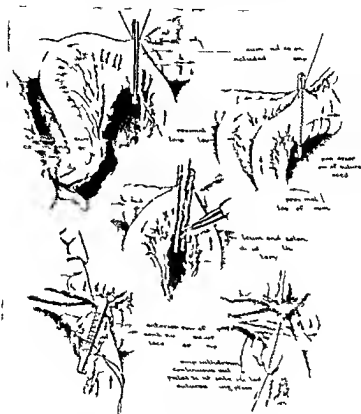


Fig 513-12 I m / Th l p f h l d h l re
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a third a resection of nearly nine feet of ileum and colon for carcinoma originating in the ileum Such one stage resections

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Fig 514—Cl p g mp ll ing b tl d m p mp d
f bd m l p r

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side. We use the fine wire universally on peritoneal surfaces, for it does not lead to peritoneal adhesions as does catgut or silk. Care should be taken to use only viable bowel ends for the anastomosis to have the sutured surfaces denuded of all fat and carefully apposed so as to be absolutely gas and water tight and to make an associated complemental appendicectomy or enterostomy. The Mikulicz operation as with any colostomy has a definite mortality from spreading pyoderma and other complications and usually even when a muscle splitting incision is used leaves a weak area in the abdominal wall.

A *four clamp method* facilitates the removal of the ileum, uterus or other organ to which the cancerous colon has attached. Two short light clamps without handles are applied on each side of the bowel lateral to the growth and the colon divided by cautery between each pair of clamps. This leaves the diseased intestinal segment clamped and attached to the uterus or other organ which then is removed or resected. The small distal and proximal clamps on the bowel to be united are now apposed over a single Payr clamp and burned off. The end to end aseptic suture is then completed over the remaining Payr clamp as described.

When the cancer has invaded an adjacent small intestinal loop it is usually feasible to fold the loop together and then apply two Payr or de Martel clamps obliquely across the base of the small intestinal loop and the attached fold of omentum which are divided by cautery between the two clamps. Lines of sutures are then placed below and above the clamp which also include the fold of omentum. The clamp is removed as the upper row of seroserous sutures is tightened. This is a simple rapid method for anastomosis and leaves a large stoma. A similar operation may be used when a cancer of the transverse colon has invaded the stomach. Again adhesions or other condition may render a combined eight clamp double resection desirable. Here the small and the large intestine are resected each with four clamps as previously described.

In resections of the colon above the sigmoid including the ileocecum one of us (W W B) has for a number of years used only end to end anastomosis. By apposing an oblique

section of the smaller ileum to a transverse section of colon a satisfactory end to end union may be made (Fig 513 1 2) A side to side anastomosis is a longer and more complicated operation the blind ends may become distended with fecal material and even open under reversed peristaltic pressure

When the cancer has invaded the anterior abdominal wall this may be resected en bloc with the diseased segment of bowel Even when the colon has perforated into the abdominal wall with the formation of a localized abscess the en bloc resection should be used if possible In one case a large carcinoma of the splenic flexure had perforated into the abdominal wall had been drained for four months elsewhere and then closed to recur three months later Even then it was possible to resect the transverse and descending colon with the large attached segment of abdominal wall enclosing the abscess and perform an end to end aseptic anastomosis between the proximal transverse colon and sigmoid over a single clamp without soiling (Fig 515) Primary union followed with the exception of a minute and transient sinus While a complementary appendicostomy and enterostomy is less often required after resection of the right colon than of the left colon it will prove life saving in certain cases and at present is our routine practice

P I P + + my

Carcinoma of the anus and lower 4 cm of the rectum may be removed by a radical perineal proctectomy To reduce a possible pelvic contamination from leakage the rectum is first packed with gauze wet with a strong hypochlorite solution By opening the peritoneum from below it is usually possible to bring down and remove at least a 7 cm margin of normal bowel above the growth and to form a perineal outlet with viable bowel Not infrequently there is so much local infiltration that it is advisable to remove the posterior vaginal wall or the seminal vesicles and a section of prostate also The end of the bowel is not sutured to the skin A rectal tube is tied into the protruding portion a curved perforated glass drain left posteriorly along the hollow of the sacrum for forty eight hours and the rest of the pelvic floor closed with

side. We use the fine wire *universally* on peritoneal surfaces, for it does not lead to peritoneal adhesions as does catgut or silk. Care should be taken to use only viable bowel ends for the anastomosis to have the sutured surfaces denuded of all fat and carefully apposed so as to be absolutely gas and water tight and to make an associated complemental appendicectomy or enterostomy. The Mikulicz operation as with any colostomy has a definite mortality from spreading pyoderma and other complications and usually even when a muscle splitting incision is used leaves a weak area in the abdominal wall.

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In resections of the colon above the sigmoid including the ileocecum one of us (W. W. B.) has for a number of years used only end to end anastomoses by apposing an oblique

buried and superficial interrupted sutures of Nos 37 and 35 alloy steel wire. As a general rule the coccyx is not excised. The operation has a low mortality (about 4 per cent) and usually a short period of hospitalization but those with anal carcinoma often have metastasis to the inguinal lymph nodes usually difficult to control by operation or irradiation. We have not seen metastasis to the inguinal nodes from intestinal carcinoma developing at higher levels.

After the operation should there be any tendency for the perineal opening to contract the patient is given a set of test tubes for daily home dilatation. By completely evacuating the colon every three days by irrigation or by a quickly acting laxative and by maintaining an adequate opening the patient usually makes a satisfactory adjustment in two or three months so that troublesome soiling is rare. In those with a tendency to diarrhea the daily administration of a pectin and kaolin mixture will usually be followed by more solid and manageable evacuations.

One Stage Abdominoperineal Operation for Rectosigmoid Cancer

In growths from the midrectum to the lower sigmoid a one stage abdominoperineal operation with preservation of the anus is preferred.

The abdomen is opened through a left oblique incision 3 cm above the inguinal ligament. The lateral leaf of the mesosigmoid is freely divided wide of any malignant infiltration and the sigmoid with attached fat and mesosigmoid mobilized toward the midline. In so doing the left ureter, iliac and the left spermatic or ovarian vessel are exposed and the spermatic or ovarian vessels divided and ligated.

On the median side of the sigmoid well above the promontory of the sacrum the inferior mesenteric and the superior hemorrhoidal vessels are identified, divided and doubly ligated. It is essential that sufficient well vascularized

Fig 515—Mrs. J. G. D. W. R. S. L. A. T. D. O. M. A. F. P. F. V. F. L. F. G. H. M. H. B. D. M. I. M. P. S. D. P. A. R. I. G. H. P. P. E. Q. D. R. F. S. M. H. G. B. S. C. E. S. S. F. B. D. M. I. W. I. L. D. R. D. H. I. D. B. F. M. H. R. R. R. E. T. B. S. C. E. S. S. W. D. M. S. E. S. I. I. G. P. O. R. T. F. B. D. M. I. W. I. L. T. H. D. B. S. E. S. E. N. D. C. D. G. L. C. L. M. P. M. H. D. R. R.



With the patient changed to the lithotomy position and the anus closed by a strong purse string suture the pelvis is entered through a curved transverse incision between the anus and scrotum or anus and fourchette. The incision curved anteriorly runs from one tuber ischi along the posterior scrotal margin to the other tuber ischi. This curved anterior perineal incision is somewhat similar to that used by Young for perineal proctectomy. It does not give as good access to structures lying back of the rectum but is convenient for any desired resection of the prostate vesicles or posterior vaginal wall.

The sphincters are divided anteriorly where the muscle is thinnest and least important; their nerve supply is not interfered with and while the resulting mechanism may not always be water tight it usually gives desirable warning of approaching defecation and a voluntary control of solid fecal masses. After incising the subcutaneous tissue the central tendon is divided just posterior to the bulb and behind the transversus perinei and the underlying triangular ligament. The rectum is retracted posteriorly and the recto urethralis muscle divided along the urethra after locating the urethra by its retention catheter. The two layers of Denonvillier's fascia are divided under the urethra; the peritoneum exposed lateral to the rectum and opened when all residual peritoneal attachments to the rectum may easily be recognized and divided. To avoid troublesome bleeding the prostate should not be disturbed unless it shows malignant invasion. The dissection is facilitated by the gauze packing or stilet tubing which was left in the rectovesical peritoneal space at the completion of the abdominal part of the operation. In women the loose fatty areas posterior to the transversus perinei and lateral to the rectum are entered by blunt dissection close to the pubococcygeus muscle; the lower rectum and vagina cautiously separated in the midline where the partition is adherent, very thin and easily perforated. Above the lower segment there is a loose cellular layer between the rectum or vagina which may readily be retracted to the peritoneum and Douglas pouch entered.

Any adjacent infiltrated tissue is divided wide of the bowel. The stilet covers on the clamped ends of sigmoid and

sigmoid be liberated (17 cm or 5 inches) to reach from the posterior pelvic brim through the perineum. Occasionally one or more of the sigmoid branches require division to mobilize the sigmoid loop sufficiently. If necessary the lateral peritoneal leaflet of the descending colon is divided and the bowel slid to a lower position. Viability is determined by observing pulsating arteries or by the character of the bleeding when the small vessels on the surface of the bowel at the level of resection are incised. The peritoneal incision is continued around the right brim of the pelvis and back of the bladder and the fat and lymphatic tissues removed from the iliac vessels, ureters and the hollow of the sacrum to the pelvic floor. Ligation of the divided middle hemirrhoidal vessels may or may not be necessary. If during the separation infiltrated tissue is encountered deep in the pelvis the dissection from the abdominal side should be discontinued and the separation completed later through the perineum.

The loop of rectosigmoid having been liberated to the pelvic floor and the mesosigmoid divided well above the tumor and any enlarged lymph nodes the liberated bowel may be divided by cauters both above and below the tumor between two short clamps of the de Martel type and the diseased segment removed. This reduces the bulk of tissue to be delivered through the perineum and particularly affords space for the formation of a pelvic diaphragm. Stockinet tubing is tied on both the proximal and distal bowel ends. A diaphragm is placed on the floor of the pelvis; a pelvic diaphragm is formed of peritoneum without tension, constriction or suture of the sigmoid and the abdomen closed.

If the loop of bowel is not excised between clamps however a ribbon of folded gauze 1 meter long which is packed against the pelvic floor and coccyx is tied about the loop of free bowel well above the growth at the level to be used for the perineal anus. The abdominal wound is then closed with buried layer sutures of No. 30 and No. 3 alloy steel wire, the subcutaneous fat with interrupted No. 35 wire and the skin with interrupted sutures of No. 35 wire and continuous No. 38 alloy steel wire. The use of wire sutures and ligatures greatly reduces the incidence of wound infection in these operations.

With the patient changed to the lithotomy position and the anus closed by a strong purse string suture the pelvis is entered through a curved transverse incision between the anus and scrotum or anus and fourchette. The incision curved anteriorly runs from one tuber ischii along the posterior scrotal margin to the other tuber ischii. This curved anterior perineal incision is somewhat similar to that used by Young for perineal proctectomy. It does not give as good access to structures lying back of the rectum but is convenient for any desired resection of the prostate vesicles or posterior vaginal wall.

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rectum are grasped through the peritoneal opening and delivered through the wound. The distal end of the rectum is resected by cautery between clamps just above the sphincters. If the proximal end has not previously been divided this section is grasped by a Payr clamp passed from without through the anus. A second clamp is applied just below the first and the sigmoid divided between with the cautery. The first Payr clamp is then withdrawn through the anal ring with the proximal end of the sigmoid. The perineal incision is closed in layers with interrupted wire sutures. Unless the anal ring is very loose about the sigmoid it is split anteriorly to eliminate strangulation of the protruding segment of bowel which is not sutured. A curved perforated glass drain is inserted along the sacrum through a stab wound at the side of the coccyx to evacuate blood and serum during the first forty-eight hours. Dressings are applied and a rectal tube tied in the protruding sigmoid. In six to seven days when the bowel has become adherent within the pelvis the rectal tube and distal bowel sloughs off. When the excess of sigmoid is burned off by cautery level with the perineum two or three days later a normal appearing functional anus connected with the sigmoid is left. These patients are often out of bed by the sixth day after the operation and able to leave the hospital by the twelfth or fourteenth day. It has the advantage over the posterior procedure of leaving no intestinal spur and of conserving the most important part of the sphincters.

The alternate method of delivery of the bowel through a posterior perineal incision does not leave as good an anal opening. After completing the abdominal part of the operation the patient is placed in an exaggerated lithotomy position. The anus is closed by a strong purse string suture and covered by an aseptic gauze pad. An incision is made in the midline from a point just posterior to the anus along the right side of the coccyx. This incision is deepened through the pelvic floor to the gauze packing which is grasped and withdrawn. The attached loop of bowel is delivered through the perineum by traction and aided by retractors the clamped bowel ends and the malignant section are eased through the opening care being taken not to disrupt cancerous tissue. The cleansed bowel is divided between clamps just above

TABLE I

S	P t g h E t	P t g A Ag G P					T t l C	
		0-29	30-39	40-49	50-59	60-69		70-79
R t m	3 0	2 3	12 2	24 4	6 7	22 9	10 6	0 8
Rect p m d	25 0	0 0	2 3	25 3	33 3	9 6	10 4	0 0
S g m d	21 2	1 2	2 4	18 9	33 8	6 9	15 8	0 0
Desc d R l	1 3	0 0	0 0	60	0	40 0	0	0 0
P l	4 1	0 0	6 6	26	40 0	26 7	0	0 0
I	3 8	0 0	0 0	14	57 4	14 2	7 1	7 1
H p t a	2 4	0 0	22 22	3 3	11 13	22 2	11 13	0 0
C m	2 2	0 0	0	23 8	28 9	38 0	9 3	0 0

TABLE 2

A	A I				411 C	C	HEL	B T	80 85
	10-0	0 29	30-39	40-49					
Amb t Pre t g	2	4	27	94	50-59	123 30	110 9 2	49 11)	2 0 55
	5	1	6 6	22 9					

the sphincters and the anal ring and sphincters split posteriorly in the midline and the withdrawn sigmoid laid in the groove thus formed.

The anterior portion of the wound but not the anus or sphincters is united by interrupted No. 3 alloy steel wire sutures and the overlying skin approximated with No. 35 wire. A curved perforated glass drain is inserted posteriorly along the hollow of the sacrum. The section of the bowel containing the cancer together with the attached fat and lymphatic tissue lying well distal to the dressing is cut away. A 28 F. rubber tube passed into the protruding loop of sigmoid secured by a ligature of silk and additional occlusive dressings applied.

The terminal ligated sigmoid with attached rectal tube sloughs off in five or six days and any protruding sigmoid is burned off to the level of the skin about the seventh or eighth day without anesthetic. This method leaves the anus divided posteriorly and of keyhole shape which in two months or more may be improved if desired by turning forward a U shaped flap formed externally along the posterior cutaneous margins of the exposed sigmoid. The sphincters, perineal muscles and skin are then united under the flap with interrupted wire sutures. If an anterior spur has formed where the sigmoid joins the anus this should be split anteriorly and sutured before raising the U shaped flap of bowel.

RESULTS

Over four hundred operations have been done without permanent colostomy. Ninety three per cent of the cases have been found to be resectable, 7 per cent inoperable. Two hundred and twelve were abdominal perineal resections with perineal anus with a recent mortality of 6.7 per cent. Of 100 patients traced after leaving the hospital 81 per cent lived one to five years, 38 per cent five to ten years and 19 per cent ten or more years.

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Obst. 75:485 (Oct.) 194

ISLET CELL ADENOMA OF THE PANCREAS

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d
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INTRODUCTION

ALTHOUGH Whipple in 1940 reported sixty-two surgical cures of hypoglycemia by removal of islet tumors, we consider the condition sufficiently rare to warrant the reporting of an additional case. This is especially true in view of the fact that in ten unselected cases from the literature the time from onset of symptoms to attempted surgical cure was 3.6 years, varying from five months to twelve years. There has been a definite delay on the part of the clinician in referring these cases to the surgeon, even when the diagnosis has been fairly definite. For example, in our case there was a delay of eight months after diagnosis was fairly well established. This is not without danger, as Frantz has reported the finding of twenty-four of these tumors at autopsy.

H to al D t

A detailed review of the literature is not indicated, as Whipple and Frantz and Wernick have published excellent review articles on the subject. However, we propose to sum-

F l D p m f S g v U r ty f P yl d
h U rs d Pl l d hl G l Hosp l
† A S rg M d l S l l U rs f P l A
d hl C b H p l l l U f P l S g Ph l
‡ A P l f D f M l l G d S l l f
¶ A C al H l l C f M l l D Ph l d l
P l A l f f S rg S l l f M l U rs ty f
S g S g Pl l d hl C l l D H p l A
S g H sp l l l U rs f P l

the sphincters and the anal ring and sphincters split posteriorly in the midline and the withdrawn sigmoid laid in the groove thus formed.

The anterior portion of the wound but not the anus or sphincters is united by interrupted No. 37 alloy steel wire sutures and the overlying skin approximated with No. 35 wire. A curved perforated glass drain is inserted posteriorly along the hollow of the sacrum. The section of the bowel containing the cancer together with the attached fat and lymphatic tissue lying well distal to the dressing is cut away. A 8 F. rubber tube passed into the protruding loop of sigmoid secured by a ligature of silk and additional occlusive dressings applied.

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RESULTS

Over four hundred operations have been done without permanent colostomy. Ninety-three per cent of the cases have been found to be resectable, 7 per cent inoperable. Two hundred and twelve were abdominoperineal resections with perineal anus with a recent mortality of 6.7 per cent. Of 100 patients traced after leaving the hospital 81 per cent lived one to five years, 38 per cent five to ten years and 19 per cent ten or more years.

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attacks. Of seventeen patients with the essential triad of symptoms mentioned operated upon by Whipple personally fifteen had islet tumors. The total number of tumors removed was nineteen as two were found in each of four cases. Of the seventeen patients one with carcinoma died on the fifth day of a pneumonia and one with adenoma died of a thyroid storm. In the thirteen tumor cases followed one patient died twenty nine months later of a duodenal hemorrhage. Twelve patients followed from four to seventy one months have all been free of hypoglycemic attacks since removal of their tumors.

Delay in surgical exploration is probably due to the none too brilliant results when no tumor is found at operation to account for the hypoglycemia. These cases present a real problem to the operating surgeon as to whether he should attempt a subtotal resection of the pancreas. It is generally accepted that partial resection is of no avail. David collected eighteen cases of partial resection with four deaths and eight showing no improvement whereas in seventeen cases of subtotal resection only four showed no improvement and there was only one death.

CASE REPORT

H + y

The patient O. S. a white male thirty eight years of age was first admitted to Doctor Dillon's service at the Philadelphia General Hospital on November 22, 1940. His past medical and social history was not significant and he was perfectly well until eighteen months before admission. At that time he was accustomed to going to work without eating any breakfast. While he was riding to work he would suddenly have clonic movements of both arms and then of the neck and if he attempted to get up he would fall to the floor. These attacks would be accompanied by sweating which was heaviest on the face but occurred from the mid chest upward. The attacks had a short prodromal period during which time he had a funny sensation in his stomach. When he fell during attacks consciousness was not lost but he was unable to speak. After having the first few at

marize briefly the history and to discuss some of the problems of hypoglycemia

Shortly after the discovery of insulin Seale Harris in 1914 postulated the possibility of hyperinsulinism Wilder and his collaborators in 1917 reported a case of carcinoma of the islets with metastases to the liver exhaustive laboratory studies were made They were able to isolate as much as 40 units of insulin from 100 gm of the tumor Howland Campbell Maltby and Robinson in 1919 reported the first surgical cure following the removal of an islet adenoma by Roscoe Graham A follow up article in 1939 reported that the patient with this original cure was still without symptoms

D g

The diagnosis of islet adenoma is based upon a characteristic triad of symptoms (Whipple) (1) attacks of insulin shock however manifested coming on during the fasting or overfatigued state (2) associated blood sugar readings of 50 mg per 100 cc or less during the attacks and (3) relief of the shock promptly following the ingestion of glucose These patients as a result of high carbohydrate intake in order to ward off attacks usually gain weight Other causes of hypoglycemia such as diseases of the pituitary adrenals thyroid and liver are not likely to produce the profound degree of hypoglycemia commonly found when a tumor of the islets is present

Pathology

The great majority of the islet tumors are microscopically and clinically benign Frantz collected a series of ninety six of which seventy were considered benign the entire one were suspected of being malignant and five were definitely malignant with metastases

Results of Operation

Whipple reports thirteen deaths in eighty two cases or a mortality of 16 per cent Of the sixty nine reported survivors five died within six months of carcinoma of islet tissue with metastases and six of the cure of their hypoglycemic

the low variety rather than the high plateau type. Blood sugar readings taken at various times during the day were never above 79 mg. During this time he had twelve shocks with blood sugar values ranging between 26 mg and 47 mg per 100 cc but generally occurring when the sugar reached 37 mg per 100 cc. His diet varied from protein 60 gm fat 80 gm and carbohydrate 170 gm to protein 170 gm fat 130 gm and carbohydrate 170 gm without any apparent influence on the number of shocks.

Except for a pathological high excretion of chlorides the laboratory tests were essentially negative as the following reports testify.

Blood count

Erythrocyte 4 380 000
Hemoglobin 16 gm per 100 cc of blood
White blood cells 12 200
Polymorphonuclears 79
Lymphocytes 19
Transferrins 1
Eosinophils 1

Wassermann test negative

Liver tests

Cholesterol 248 mg per 100 cc of blood
Cholesterol esters, 111 mg per 100 cc of blood—49 per cent

Van den Bergh indirect negative

Icteric index 10

Bromine sulfalein test no retention

Alkaline phosphatase 2 units

Urobilinogen 4.5 mg per 100 cc of blood

Hippuric acid 2.6 gm of benzoic acid

Grubbs-Cole test normally functioning gall bladder

Printz neurolgic reaction negative

X-ray of skull all normal in shape size and outline

Visual field and eyegrounds normal

Thoracic basal metal rate plus no enlargement

Pancreas sugars as reported blood glucose 32 cc

Urea N 20.5 OH amylase 79

Adrenal

Blood cholesterol 585 mg per 100 cc

17-OH corticosteroids 1-540 mg —410 mg 3-819 mg

tacks he consulted his doctor who advised him to eat breakfast and to carry sugar with him and eat it in case of shock. No further shocks occurred in the mornings but occasionally he would have profuse sweats and weakness at about two or three o'clock in the morning. The attacks were relieved by sugar ingestion. When the patient was not working he had no shocks.

Because he continued to have occasional shocks often occurring after hard physical labor he was referred to another hospital where he was observed periodically but so far as he knows no studies were made to determine the etiology of his hypoglycemia.

About four weeks before his first admission the patient began having shocks about four o'clock almost every afternoon despite fairly heavy sugar ingestion. Four days before admission he had a severe shock and fell to the floor. This was his last before admission. His dietary intake had been heavy consisting of a large breakfast cake and beverage at 10 A.M., lunch at noon, ice cream and cake at 3 P.M., supper and then something before he went to bed. In addition he had been taking three heaping teaspoonful of sugar in water five or six times a day and he always carried lumps of sugar with him. He gained about 40 pounds under this regimen weighing 195 pounds on admission.

Examination

The patient had no complaints of pain, no headaches and no vertigo. He stated that at about 6:30 to 7 P.M. his vision frequently became blurred while reading. A decrease in libido for the past two years had been his only other symptom.

Physical examination was essentially negative. His pulse varied between 70 and 100 during his stay in the hospital from November 22, 1940 to January 9, 1941. Blood pressure in mm. of mercury was 144 systolic and 80 diastolic. The impression given at this time was spontaneous hypoglycemia of unknown etiology.

The patient's fasting blood sugar values varied between 50 and 75 mg. per 100 cc. The glucose tolerance curve was of

The patient's condition was excellent throughout the operation and remained so on his return to the ward. For the first thirty six hours he was given fluids parenterally, thereafter he received food by mouth. The blood sugar during the period of intravenous infusions was 200 mg per 100 cc but on the third postoperative day fasting blood sugar was 113 mg and varied between that and 84 mg during the next fifteen days. The wound healed by primary intention. The patient was discharged from the hospital on August 9, 1941 and has remained well until August 20, 1941 on which date he was discharged from Metabolic Clinic and given a note saying he was well enough for service in the armed forces of the United States.

Pathologic report by Dr. H. M. Dixon. An oval shaped slightly lobulated structure measuring 3.5 by 2.5 by 2.3 cm. It is covered with a thin smooth layer of connective tissue except on one side where on the cut surface a small amount of dark gray pancreatic tissue is seen. The other surfaces are dark reddish purple with a few strands of adipose tissue in some places. The general consistency of the specimen is somewhat cystic but sectioning reveals no cystic areas and resistance to cutting is relatively slight. The cut surface shows a rim of dark red tissue surrounding a well defined nodule, gray uniformly reddish gray, oval shaped area 2 cm in length and 1 cm in diameter at the widest point. The consistency of this portion is approximately the same as that of the surrounding tissue. Section through the midpoint of the specimen including the capsule shows a narrow rim of compressed pancreatic tissue separated from a central mass of cells by a thin layer of connective tissue. These cells are arranged in small islands of irregular size that are separated from one another by a delicate connective tissue network containing numerous thin dilated vascular spaces. The cells are round and polyhedral, contain a considerable amount of granular nonvacuolated pale pink staining cytoplasm and have fairly large round and somewhat oval shaped nuclei that for the most part are deeply stained by the hematoxylin. No definite mitotic figures are seen. The apparent encapsulation and general infiltration of the cells and nuclei would indicate a benign type of tumor and from the gross appearance it would seem that it had been entirely removed.

Diagnosis: Adenoma of islet tissue of the pancreas.

Excretion again 1-398 mg 2-70 mg 3-688 mg

Flat pit of abdomen showed kidneys normal in size and no definite calcification in the region of the adrenals

Lumbar spine and bones of pelvis normal

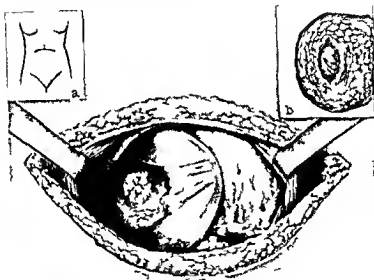
Concurrent Therapy

Because of the abnormality in chloride excretion the patient was discharged on trial of high chloride intake and cortin. Following discharge on a diet of protein 170 gm fat 130 gm carbohydrate 10 gm and cortin he was well for six weeks. Shocks gradually began again occurring once or twice a week. The patient was finally readmitted for exploratory laparotomy on July 15 1941. The only change noted was a rise in blood pressure to 147 systolic and 78 diastolic.

Operation

On July 27 1941 exploration was performed under continuous spinal anesthesia with a venoclisis of 5 per cent glucose running simultaneously. A transverse incision was made about 1/2 inches above the umbilicus. Both rectus muscles were divided transversely. The lesser peritoneal cavity was entered through the gastrocolic omentum. The body and tail of the pancreas were readily exposed and no tumor could be seen or palpated in it. The head of the pancreas was then palpated and an indefinite cystlike mass was felt. This was exposed by cutting the peritoneum and reflecting the duodenum medially. A mass could be seen and felt in the head of the pancreas but no typical islet tumor appeared. However on incising the head of the pancreas a definite circumscribed reddish purple adenoma was exposed which could be readily differentiated and shelled out as easily as a lipoma. The exposure obtained by this incision was excellent and made the procedure rather simple. Silk was used in ligating the vessels in the pancreas. Catgut was used in closing the gastrocolic omentum and in replacing the duodenum. The peritoneum and posterior rectus sheath were closed with interrupted sutures of catgut. The anterior rectus sheath was closed with wire and tension sutures of wire and the skin was closed with clips. No drains were inserted.

terized by a purplish pink nodule 1 to 2 cm in diameter usually standing out distinctly from the whiter pancreatic tissue and covered with fine vessels which bleed easily but are readily ligated. The adenoma is usually encapsulated and is shelled out without difficulty after the small vessels have been ligated with the finest of silk ligatures.



I g 516-I er () L f l d m l C p f
l l p d l d l g l d d m m ll
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ert (b) e l f tu f pl g h rm l p g

In our case as in many others in the literature the adenoma was not on the surface of the gland. The pancreas covering the adenoma was normal in appearance and only after splitting the normal overlying tissue did the typical adenoma present itself.

If the adenoma is discovered search should be made for others. If no adenoma or adenomata are seen on the anterior surface the pancreas should be mobilized by incising its inferior peritoneal attachment and gently elevated inspected

SURGICAL THERAPY

Whipple has outlined a course of therapy which contains the practical facts essential to the practicing surgeon so that we feel justified in repeating it here almost verbatim. We also wish to add several minor suggestions which we feel will contribute to the smooth handling of these cases.

After the diagnosis of chronic hypoglycemia is established and hepatic and pituitary causes have been ruled out the patient should have a course of medical therapy of three to four weeks to determine the response of the individual to conservative measures. If it is found that the blood sugar values are continuing to remain low and that the seizures are controlled only on a high carbohydrate intake an exploratory celiotomy is indicated.

Whipple suggests spinal anesthesia because complete relaxation is essential. We feel that this should be modified to Lemmon's continuous spinal technique. This gives the surgeon adequate leisure for a thorough and complete exposure of the pancreas.

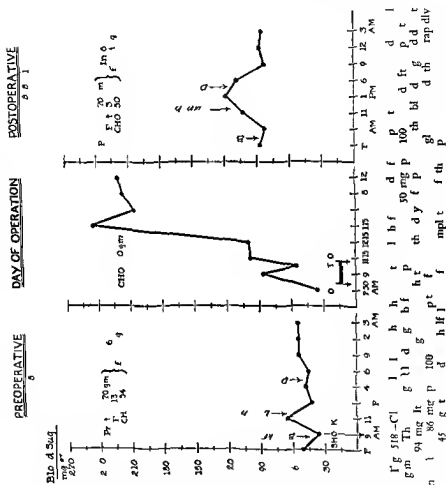
Guerry and McCutcheon found that atropine lowered the blood sugar rapidly in one case of hypoglycemia. We mention it here in view of its almost universal use in preoperative hypodermies and recommend that it be definitely interdicted.

A wide transverse incision including both recti provides by far the best approach. A left split rectus fails in the majority of cases to give adequate exposure. A wide division of the gastrocolic omentum exposes the entire pancreas to inspection and palpation—head, body and tail.

This view is not quite adequate as Whipple's four cases of subtotal resection of the pancreas in which he later found adenomas in the head clearly indicate. Fifty per cent of the fourteen tumors missed at first operation occurred in the head. Further exposure of the head is best accomplished by mobilizing the duodenum by incising the peritoneum lateral to it. This is shown clearly in the accompanying diagram (Fig. 516). Exploration of the pancreas by palpation without exposing the gland is mentioned only to be condemned.

The typical gross appearance of the adenoma is charac-

do he would ligate the splenic artery because of the difficulty in dealing with the bleeding of its branches going into the pancreas Doctor Thomason did this which of course



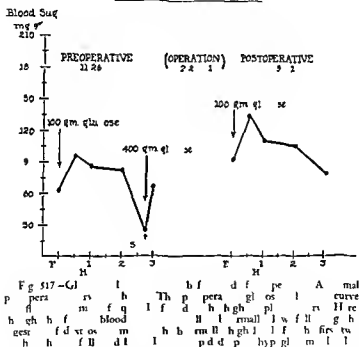
necessitated a splenectomy as well but the ligation of the splenic artery rendered the operation practically bloodless and the mechanical features were greatly simplified. He removed the tail and fully excising the pancreas with a Percy

and palpated on its posterior aspect. Hemorrhage is most apt to occur around the head.

Adenomata are most frequently found in the tail and body and should be looked for in these areas first.

As suggested above we believe the most satisfactory results will be obtained in complete exposure of the whole gland in all cases.

GLUCOSE TOLERANCE CURVES



If no adenoma or adenomata can be seen or felt the next most effective measure is the removal of at least two thirds of the pancreas—that is the tail and body—leaving the portion of the head in the curvature of the duodenum. Doctor Thompson in a personal communication says that in his operation he followed the suggestion of Doctor Emmet Mann of San Francisco. He stated that if he had another case to

cautery searing the end very thoroughly. A Penrose drain was used but there was no discharge and the patient made an absolutely uninterrupted recovery with primary wound healing.

A drain should be placed down to the bed of the pancreas if the organ is resected to provide for oozing or a leakage of pancreatic juice. As a rule the site of an enucleated adenoma does not have to be drained.

Silk technic using the finest grade of silk for ligatures of small vessels and a slightly heavier grade for the larger vessels and the rectus sheaths has given us perfect wound repair. The silk in the rectus sheath may be replaced by fine alloy steel wire.

Guerra and McCutcheon report an instance of death on the table presumably from hypoglycemia. It is our custom to give a continuous intravenous infusion of 5 or 10 per cent glucose throughout all major procedures under continuous spinal anesthesia and because of reported fatality we wish especially to emphasize the value of this procedure.

SUMMARY

Another successful case of removal of an islet adenoma has been reported.

Three suggestions have been offered in addition to Whipple's excellent outline of surgical therapy: (1) the use of continuous spinal anesthesia; (2) this should be supplemented by a continuous venoclisis of 5 or 10 per cent glucose; (3) the head of the pancreas should be exposed by mobilizing the duodenum and rotating it to the left side by incising the peritoneum between it and the liver.

Emphasis has been placed on thorough exploration of the pancreas including the head by direct vision as well as palpation in all cases of suspected hyperinsulinism.

Attention has been called to the delay in diagnosing these cases and also to the hesitancy on the part of clinician in referring them for operative treatment after diagnosis is established. Reports of death in case in which operation as performed warrant early surgery.

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PANCREATIC CYST REPORT OF FIVE CASES

THOMAS A JOHNSON MD FACPT

d

WALTER E LEE MD FACST

ARCHIBALD AND KAUFMAN divide pancreatic cysts into four groups

- 1 *Adenocystoma* True pancreatic cysts lined with cuboidal epithelium Usually ferments are absent in the cystic fluid
- 2 *Retention cysts* The result of obstruction of one of the smaller pancreatic ducts due to calculi tumor or scar tissue Recent n cysts are small and are associated with interstitial pancreatitis
- 3 *Degenerative cysts* The end results of localized acute pancreatic necrosis with softening and cystic transformation of the destroyed pancreatic tissue Degenerative cysts occur within the substance of the pancreas
- 4 *Pseudocysts* Etiologically and morphologically similar to degenerative cysts but occurring outside the main body of pancreatic substance usually in the lesser peritoneal sac They may contain blood inflammatory exudate and small amounts of pancreatic fluid

For purposes of orientation Fig 519 from an article by Case illustrates the usual roentgenologic aspects of these pancreatic cysts and Fig 520 (also from Case) shows the relation of pancreatic cysts to the abdominal viscera

F	th	D p rtm	f G	-e	l gy	d S	g ry	G d t	t
Sch l t M d	U	rs ty	f P m n y l			d th	Grad t H		
p l f h U	rs v	f P	yl						
† Assoc	G st o-e	logy	Grad t	Sch l	f M d		Unu		
rs ty f P	yl	Assoc	G	-e	logy	Grad t	Hosp tal		
† Prof ss	f S rgery	Grad	School	f M d		Unu	rs ty f		
P l s	Ch f f h	Surgical Serv	Gradua	Hosp	l f h U				
rs ty f P	yl	d G m	wn	Hosp	l S rg	Brvn M w			
d Ch ld	Hosp tal								



Fig 519-V roe g l g p f p cyst / ga ro-
 h p type 2 y f h d f p as 3 st f l f p rea 4
 t f b dy f p f gast oc l typ 6 mes oc l type (Af
 P r d R rs from Case in Am J f Roe d R d Th rap
 V l 44)

We are reporting the clinical features of five cases of pancreatic cyst observed at the Graduate Hospital in the past

TABULATION

SEX	S	T F	R	I x C	P	C	
Case	Age (yr)	Sex	Diagnosis	Immunologic	Operation	Pathologic	
I H C	3	I	Italy	P	resected	E	lymphoma
II M D	48	F	Italy	Generalized	Laparotomy	Perse	lymphoma
III V B	7	F	Italy	Probable	Laparotomy	Perse	lymphoma
IV M S	39	F	Italy	Epigastric	Laparotomy	Perse	lymphoma
V I R	68	F	Italy	Malignant	Laparotomy	Perse	lymphoma

Case I

H C fen le The past medical history was unremarkable except for asymptomatic minimal tuberculous lesions at both lung apices.

The onset of the present complaint began with three isolated attacks of moderately acute epigastric pain six months, one month and two weeks prior to admission. Each attack lasted one to three days and was associated with nausea and vomiting. After the third attack slight distress persisted for about one week. Food ingestion caused some epigastric discomfort therefore the patient restricted her diet and her weight decreased from 139 pounds to 117 pounds. Apart from moderate constipation controlled by proprietary laxatives the patient had no other complaints.

The physical examination was negative except for the presence of a lemon-sized hard smooth mass in the left epigastrum which descended with inspiration and was slightly tender.

Postoperative examination of the stomach disclosed a circumferential defect along the greater curvature of the stomach at its midportion apparently produced by a traumatic mass protruding from the nature of a peptic ulcer arising in the tail of the pancreas, or cyst of the pancreas. The proximal jejunal distal to the duodenum appeared compressed by an extrinsic mass (Fig. 5 I).

The following operative note was made by Dr Lee Under spinal anesthesia the abdomen was opened through a left rectus incision and we could feel the tumor in the lesser peritoneal cavity before we divided the gastrocolic omentum. The stomach was not involved in any way there was no glandular involvement of any kind and the tumor was cir



l g f l (Ca I) -R g gram h g fill g d f
 l g l g f l m h ts m dp rt pp ly
 l f b m ss Th p m l j l m d st l h d
 d j l fl pp rs p d by ri m ss

umscribed almost circular in shape and about 4 inches in its greatest diameter. We were able to separate the duodenum to which it was tightly adherent for its entire length and we found that the tumor occupied one half of the body of the pancreas and all of the tail and it was decided to enucleate it rather than to drain it. We were able to free it

TABULATION

SUMM. S IE Y F R S IN FIVE C ES P RE C

C se	Ag (years)	Se d D n at	Proce t D gn	Operat
I H C	3	I t h	P t c y t	E ci f yst
II M D	48	I sh	Ge ralized bd m al malign y	Lapa t my Fesse cath t pl d pa reat y t
III V B	77	F Itah	Probabl cyst I th p cr	Laparot my Fesse cath t pla ed pa re t y t
IV M S	39	F C l d	Ep gast mas sec d ry t cut	Ch l y t t my Dra na f p t c y t
V I R	68	F J h	M l gna cy f th p m b l d t	Ch l y t)) t my Fesse cathe- t placed pa c y t

Case I

H C fem le The past m dic l h tory as irrele ant e cept for asymptomat c m num l tuberculous lesio s at both lung ap s

The onset of the present omplaint beg n vith three isol ted attacks of moderately acute ep gastric pain six months one m th and two v eeks pri r to admiss n Each att ck lasted one t three days nd v as a oc ted ith nausea and vom ting After the third attack l ght distress persisted for ab ut ne eek Food ingest n caused me ep ga t c discomfort, therefore th pat nt r tricted h r d et a d h r e oht deer sed from 139 p unds to 17 pounds Ap rt from moderat con tipat n c n troll d by propr et ry laxat es the pat nt had no ther c m plants

The physical c minat on as neg t e cept for th pes ence of lem n sized h rd, sm oth m s in th left ep gastrum v hch de cend d with nspiratio nd as sl ghtly tender

R entgenol g c xam n t n of th st m h d l d a on vey fill ng def ct al ng the g ater c rvatu of the st mach at its m dport on, apparently pr d ced b n e trins m ss, p l bly of the natu f a p ncreat c cyst ri ng n the tal of the p n reas, or a cyst f th mesent ry Th pr m l jejunum d s tal t the d oden j un l flexu e ppear c mpress d by a v tr ns c mass (Fg 521)

The origin of this cyst is uncertain. The pathologic report suggests that we were dealing with a true cyst lined with epithelium.

CASE II

M. D. female. The past medical history was irrelevant except for the removal of an acutely inflamed appendix seven years prior to the present hospital admission. At the time of her initial visit the patient described the following complaints: (1) a tendency for the abdomen to become distended with gas intermittently for the past five years; (2) for the past two months generalized abdominal pain radiating to the back coming on initially after meals and later becoming almost constant; (3) loss of weight from 107 to 90 pounds in the past year. The weight loss began before the onset of anorexia; (4) anorexia; (5) very slight constipation.

Apart from obvious evidence of malnutrition and weight loss on physical examination Dr. Boelzli noted the following: (1) a palpable mass in the left epigastrium descending below the rib margin with inspiration to the left of the xiphoid cartilage laterally to the midclavicular line; (2) a deep mass posteriorly in the region of the left kidney; (3) a mass encroaching on the rectal lumen from the region of the cervix; (4) a palpable spleen.

Apart from a moderate secondary anemia the following studies were normal: Wassermann serum bilirubin, blood sugar (90 mg. per 100 cc. of blood), urine, fractional gastric analysis. Two serum lipase determinations were normal. Bromsulfalein (1 mg. dose) 10 per cent retention in thirty minutes. The stool showed a +4 reaction for occult blood (Griegersen).

Roentgenologic examination prior to hospitalization showed a single negative defect throughout the body of the stomach which was believed to be due to the effect of an extragastric mass. Intracoenography was negative except for evidence of some deformity in the outline of the urinary bladder evidently due to extrinsic pressure by the uterus.

Dr. Lee performed a laparotomy and found a generalized carcinomatosis of the abdomen. A definite tumor mass encroached on the greater curvature of the stomach but the tumor had spread widely into the peritoneal tissues and there were small masses of metastatic tissue in the viscera and peritoneum. A cystic mass in the pancreas was punctured.

from the end of the tail (its left edge) and on its inferior surface and from the deeper tissues. The splenic vein was unusually large and we had some difficulty controlling the bleeding from this vein. However lateral sutures accomplished this and then we cut the pancreas across at about the junction of the right third with the middle third. The cut surface of the pancreas was ligated with multiple chromic catgut sutures. At the close of this procedure the wound was perfectly dry and we placed a rubber dam drain into the cavity and brought it out through a stab wound in the left flank. This was necessary because in order to expose the splenic vein adequately we cut the cyst away and left a small portion of the cyst wall attached to the splenic vein rather than try to isolate it completely and further injure the wall of the vein as we had done at the tail. The laparotomy wound was closed by continuous sutures. The skin and subcutaneous tissues were approximated by vertical mattress sutures of black silk.

Postoperatively the patient did well. The drainage from the site of the tumor gradually subsided and the patient was discharged twenty four days after operation.

The microscopic examination of the cyst wall is reported by Dr. E. A. Case follows. The cyst wall is fibrous and in this fairly dense tissue there are a number of islands of pancreatic tissue. The cells of the islands are granular, some are vacuolated and in areas groups of cells are necrotic. The cells are more widely separated than usual. The cyst lining has evidently been epithelial but the epithelium is mostly destroyed.

At no time during her hospitalization did the patient show any alteration in her blood chemistry. Preoperative and postoperative fasting blood sugar determinations were 87 and 8 mg per 100 cc of blood. Eight day postoperatively the serum lipase is 1 cc of twentieth normal sodium hydroxide per 1 cc of serum a moderate elevation probably referable to surgical trauma of the pancreas. Unfortunately a preoperative serum lipase determination was not made. The patient has remained symptom free for ten years since her discharge from the hospital.

Dr Lee operated on the patient three weeks after admission to the hospital. A large cyst of the pancreas was partly isolated through an approach by way of the gastrocolic omentum. A smoky colored clear fluid amounting to 970 cc was aspirated from the cyst together with 15 cc of a muddy



Fig 32 (Ca III) - Roentgenogram of the abdomen showing the pancreas and the cyst.

gray material. A Pesser catheter was introduced into the cyst cavity for drainage and allowed to emerge through a stab wound in the left flank after passing through the descending mesocolon. The integument surrounding the stab wound was protected from the digestive action of the cyst fluid by the liberal use of aluminum paste.

and a Pesser catheter introduced. The fluid from the pancreatic cyst was deeply tinged with blood. A small piece of hepatic tissue was removed for microscopic examination. The patient followed a gradual but consistently downhill course postoperatively and expired four months after operation. A microscopic examination of the liver specimen showed adenocarcinoma. The sediment of the peritoneal fluid contained large cells which Dr. Case believed were cancer cells.

The malignant pancreatic cyst would seem to represent merely an incidental finding in this case of widespread abdominal malignancy. The fact that both the cyst fluid and peritoneal exudate were bloody suggests that the former was malignant in origin although no specimen of the cyst wall was obtained. A specimen of the cyst fluid was tested for lipase which was absent. Two determinations of serum lipase prior to operation were normal.

Case III

A seventy-seven-year-old woman, as seen by her family doctor five months before admission, at which time she suffered cramp-like oppression in the upper right quadrant. She continued to have similar mild pain up to the time of her admission to the hospital. There was some anorexia and weight loss (10 pounds). She took only small amounts of liquid during that period because of a tendency to regurgitate solid food. Three weeks before admission the pain seemed more severe. Eight days before admission the blood sugar was 86 mg per 100 cc and the patient was sent to the hospital for further study and treatment at the end of her dietetic treatment.

Physic examination revealed a globular, soft, nontender, highly mobile, half grapefruit-sized, palpable mass in the upper right quadrant, extending some distance to the left of the midline and not descending through the navel.

A moderate secondary anemia was found. The urinary protein, blood hematuria, and uric acid were normal. The fasting blood sugar averaged 190 mg per 100.

Two weeks after admission the serum lipase was 144 c.f.u. (normal 0-150) and the serum amylase was 100 (normal 0-100). The patient was examined by a gastroenterologist and a small amount of gastric juice was obtained from the stomach. The pancreas was not palpable. The tumor was suggested (Fig. 5-2).

lipase values. The patient remained a mild diabetic postoperatively during a two year follow up.

Case IV

M. S. female. For six years prior to hospitalization the patient had been studied in the out patient neuropsychiatric clinic with a diagnosis of globus hystericus. One year prior to hospitalization a diagnosis of cholelithiasis was made in the gastrointestinal clinic on the basis of oral cholecystography showing a well functioning gallbladder containing many nonopaque calculi. A surgical biliary drainage in the clinic demonstrated calcium bilirubinate and cholesterol crystals in the recovered material. The patient refused operation at that time. Two weeks before hospitalization she developed a severe attack of biliary colic which continued to the time of her admission to the ward with upper right quadrant and epigastric tenderness and rigidity, fever, leukocytosis, slight hyperbilirubinemia and hyperlipasemia. One week later after the acute attack had subsided some of the medical staff palpated a round tender epigastric mass. Two weeks after admission a barium enema showed some downward displacement of the midtransverse colon probably due to extracolonic pressure from the (Fig. 53).

Three weeks after admission Dr. Lee operated and made the following notes: Under intermittent spinal anesthesia we opened into the upper right abdominal quadrant with the usual subcostal incision for exposing the gallbladder. The gallbladder was found to be filled with small stones, the wall was somewhat thickened but there was no evidence of recent acute inflammation. The liver was normal in color, the edges thin and there were no gross signs of hepatitis. The mass, about the size of a large navel orange but shaped more like a pear with the greatest enlargement to the right was in the lesser peritoneal cavity and adherent to the gastroduodenal omentum. It was not movable but was fixed to the retroperitoneal tissues. It was much larger to the right near the head of the pancreas than in the midline where it was somewhat cystic. A needle put in this area however obtained slate colored fluid in small quantities but upon opening through the very thin wall we entered a cyst which was about the size of a small walnut. It contained some gangrenous slate colored

Dr. Case reported that the biopsy of the cyst wall showed fibrous tissue with scattered cells of a chronic inflammatory reaction. He was not able to indicate the probable origin of the cyst. The contents of the cyst were entirely necrotic and no cellular element was present.

Postoperatively the wound drained profusely through the Pesser catheter. Throughout the postoperative period there was a mild febrile reaction. The patient was discharged four weeks after operation. There remained a small amount of drainage from the stab wound at the time of discharge from the hospital. The patient was readmitted some months later for a persistent sinus which finally healed.

The presence of distress in the upper abdomen for four months prior to admission in an elderly female who had complained of no previous symptoms suggests that a low grade pancreatitis may have caused obstruction to the flow of pancreatic secretion sufficient to give rise to a retention cyst. The elevated blood sugar which was first noted a week before admission lends support to that idea. Ten days before operation a serum lipase determination as reported as 144 cc of twentieth normal sodium hydroxide per 1 cc of serum a value slightly in excess of our top normal (1 cc). Serum lipase four days after operation as normal a value which may be related to the minimum amount of trauma to which the main body of pancreatic tissue was subjected at operation.

A specimen of the cyst fluid was saved at the time of operation. The fluid was turbid but cleared after centrifuging. Microscopic examination of the sediment revealed calcium bilirubin pigment. A determination of the sugar content of the cyst fluid using a blood sugar technique was reported as 116 mg per 100 cc. A lipase determination (1 v method) showed about one tenth the amount usually found in pancreatic secretion removed from the duodenum. A lipase determination using the technique for serum lipase as reported as 8 cc of twentieth normal sodium hydroxide per 1 cc of cyst fluid a very high value. The latter determinations may be misleading because one would expect high lipase values in the fluid of a retention cyst of the pancreas. The cyst fluid should be compared to duodenal lipase values rather than to serum

pouch and the laparotomy wound was closed by layer sutures of catgut

A specimen of the cyst fluid removed at the time of operation was examined. The cyst fluid was brown thick and contained some heavy flocculent material. An estimation of lipase activity on the basis of that usually regarded as normal for duodenal contents revealed no activity.

This case probably represents an acute pancreatitis which caused necrosis of a portion of the pancreas. The presence of gallstones had been noted prior to the onset of the acute illness. Repeated examination of the stomach and duodenum by barium meal during the study of the patient in the outpatient department showed no gross abnormality. The epigastric mass first was noted at the end of the first week of hospitalization. It is fair to conclude that the mass followed her attack of acute pancreatitis.

There were eleven determinations of serum lipase

6/9/40	Adm	t	th	w	d
6/10/40	3.74	N/20	N	Oil	
6/12/40	2.90				
6/17/40	1.52				
6/19/40	1.74				
6/22/40	1.52				
6/24/40	1.62				
6/27/40	0.80				
7/1/40	Op	t			
7/2/40	0.56	N/20	N	Oil	
7/13/40	0.64				
7/22/40	0.20				
7/24/40	0.32				

The above values roughly corresponded with the clinical condition of the patient. The serum lipase value did not fall within the normal range (below 1 cc) until eighteen days after admission and three days before operation.

Cas. V

I. R. a sixty-eight year old Jewish woman was admitted to the Graduate Hospital in a confused mental state complaining of nausea and a skin rash. The nausea had been present for the past few weeks. There had been no vomiting. There were severe fluctuating abdominal pains attributed to slight constipation. The rash was of two weeks duration and involved chiefly the trunk.

material such as one sees in pancreatic cysts. The remainder of the tumor mass was composed of solid tissue which probably was a diffusely enlarged pancreas. The gastrocolic omentum contained numerous areas of fat necrosis and we felt that this patient had had an acute hemorrhagic pancreatitis.



Fig. 53 (Ca IV) - Roentgenogram of the midtransverse section of the abdomen showing a large, dark, irregular mass in the upper abdominal region, possibly representing a pancreatic tumor or cyst. The surrounding areas are lighter, showing some anatomical structures like the spine and ribs. The image is grainy and has a high level of contrast, typical of older medical photography.

with a hemorrhage which had broken down and formed this cyst. This cavity was drained with vaseline gauze after evacuating and removing some of the tissue. The gallbladder was removed. A stab wound was made in the right flank through which a rubber dam tube drain was passed into Morrison's

could be seen when the gastrocolic omentum was put on tension and it definitely encroached upon the lesser curvature in the prepyloric region and may have been the cause of the distortion of this area which was referred to by the roentgenologist. The cyst in the head of the pancreas seemed to be covered with normal pancreatic tissue. It was about $1\frac{1}{4}$ inches in diameter. We tried to isolate it but in doing so we entered the cavity and found that it extended the entire length of the pancreas and contained 7 ounces or more of a clear watery fluid. The cavity was drained with a Pesser catheter after removing a section from its wall and then an end to side anastomosis was made between the fundus of the gallbladder and the antimesenteric wall of the jejunum about 3 feet distal to where it emerged from the ligament of Treitz. This was a more formal anastomosis than we usually perform and three layers were used posteriorly and two anteriorly. My impression was that there was some form of obstruction in the region of the ampulla of Vater which was pressing upon the opening of the pancreatic duct as well as that of the common duct. We could not feel anything in this region which suggested a stone.

An examination of the fluid draining from the cyst through the Pesser catheter showed about one third the amount of lipolytic activity one normally expects in duodenal contents.

The patient was discharged from the hospital twelve weeks after admission which was six weeks after her operation after a relatively uneventful convalescence.

The preoperative clinical picture in this case was confusing. The serum bilirubin on admission (3.6 mg per 100 cc) was not indicative of a complete biliary obstruction. Moreover the fall in serum bilirubin values to 0.8 mg was not consistent with malignancy either of the common duct, ampulla of Vater or head of the pancreas. The size and consistency of the gallbladder did not change during the preoperative period. The moderate diabetic tendency persisted as evidenced by the continued elevation of the fasting blood sugar. The brom sulfalein retention was higher than one would expect with this degree of biliary obstruction. The roentgenologic appearance of the stomach suggesting an

and extremely. There was a loss of 15 pounds in the previous few months.

Apart from emaciation the physical examination was negative except for the presence of a hard rounded mass in the lower right abdomen which appeared to be the gallbladder.

Laboratory studies showed a nondiabetic secondary anemia. The fasting blood sugar varied to 150 mg. per 100 cc. of blood. The blood urea nitrogen, carbon dioxide combining power, blood cholesterol, serum phosphatase and serum protein were within normal limits. The serum bilirubin was 3.6 mg. per 100 cc. on the patient's admission. Five weeks after admission the serum bilirubin was 0.8 mg. per 100 cc. The bromsulphalein test (2 mg. per kilogram of dose) showed 50 per cent retention in thirty minutes three weeks after admission and 5 per cent retention one week later. The stools showed an occult blood trace. Of occult blood. For determination of the serum lipase were within normal limits.

X-ray examination of the stomach and duodenum showed no distortion of the antral mucosa, the suggestion of which could not be determined. The distal end of the pylorictrum failed to fill out. Pyloric stenosis present in this area but the field appeared stiffened. It was impossible to exclude ulceration in the prepyloric area as a possibility.

Six weeks after admission Dr. Lee operated on the patient. The following observations were recorded by Dr. Lee.

There was a very large and elongated gallbladder the fundus of which reached the level of the crest of the ilium. It was 21 inches in diameter and the walls were not inflamed. There were adhesions in the foramen of Winslow which were easily separated and with the forefinger in the foramen of Winslow the common duct could be palpated. It contained no stones and apparently was not enlarged. The liver was chocolate colored and although the edges were sharp it was beginning to show signs of cirrhosis and the under surface had a definite nodular appearance. However the density of the liver did not seem to be increased. The stomach to gross appearance was normal but in the lesser omental cavity one could feel an enlarged pancreas. This enlargement apparently involved the entire length of the pancreas and in the head there was a cystic enlargement which

THE FATE OF TRANSFUSED REFRIGERATED BLOOD AND THE PROBLEM OF BLOOD BANKS

MAX M. STRUMIA, M.D., D.S. (M.D.)†

EARLY attempts at preservation of blood of animals and humans have been reviewed by Jeanneney, Servantie and Viero, and others. The first practical contribution to our problem is that of Robertson of the United States Army, who during the first World War, using the method proposed by Rous and Turner in 1916, transfused twenty patients with blood preserved up to twenty-four days. Of the twenty patients, nine died. The author states that the survivors owed their lives to the transfusions.

The contribution of a group of Russian workers experimenting with animal and human blood from cadavers as well as from living donors brought the whole subject to the fore. Among this group must be mentioned Burdenko (1911), Shamoff (1928), Samov and Kostriakov (1929), and finally Judine and his co-workers.

The use of cadaver blood, aside from any debatable sentimental reason, serves no practical purpose. Concerning the placental blood, the difficulty in obtaining it, the small average yield (75 cc.) and type of blood obtained make its use both expensive and impractical.

Our problem will therefore be limited to the study of preserved blood obtained from living donors.

PRELIMINARY CONSIDERATIONS

In this country, following the publication of Fantus, reports of blood banks were established in many institutions.

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tral distortion was consistent with the diagnosis of an encroaching lesion arising from the pancreas. The presence of a pancreatic cyst at operation explains only a portion of the preoperative findings. The antral distortion, diabetes and moderate hyperbilirubinemia could be explained on the basis of pancreatic changes secondary to some sudden enlargement of the cyst or inflammation of the surrounding region which had subsided. The persistently enlarged dilated gallbladder in the presence of a normally appearing common duct is not explained on the basis of the operative findings, particularly in view of the preoperative drop in serum bilirubin to 0.8 mg per 100 cc.

SUMMARY AND CONCLUSIONS

In conclusion several interesting clinical features are noted in our series of five cases of pancreatic cysts:

1. All the cases occurred in females.

The ages varied from thirty-five to seventy-seven years.

3. In three cases a preoperative diagnosis of pancreatic cysts was made largely on the basis of roentgenologic observations.

4. Only one case was associated with malignancy and in that case the only death in the series occurred.

5. Three cases showed a diabetic trend.

6. Three cases showed abnormalities in the serum lipase concentration.

7. In one case the cyst was excised. In the other four cases the cysts were drained externally by means of a Pesser catheter. In no instance was there any degeneration of the integument surrounding the stab wound through which the Pesser catheter drained.

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Posttransfusion Reactions

Reactions Following Transfusions of Fresh Citrated Blood

—In six years from 1932 to 1937 inclusive over 1500 transfusions of fresh citrated blood were performed at the Bryn Mawr Hospital. Out of this number there occurred only one death attributable to transfusion reaction and one other severe reaction. The death occurred in a patient with hemolytic jaundice—a disease in which blood transfusion as in all diseases with accelerated blood destruction is often attended by severe hemolytic reactions as Greppi (1926) and more recently Sharpe and Davis have pointed out. The severe reaction occurred in a patient suffering with a tuberculous empyema with superimposed streptococcic infection. Continuous drainage of large quantities of purulent exudate had resulted in a severe hypoproteinemia—a condition in which I had previously noted a severe reaction with oliguria and azotemia following transfusion. Thus over a period of six years the mortality from transfusions in the Bryn Mawr Hospital had been less than 0.07 per cent which compares favorably with DeGowins' reported mortality of 0.2 per cent in 3500 transfusions at the Hospital of the State University of Iowa and Tiber's death rate of 0.13 per cent in 1467 transfusions at the Bellevue Hospital. Rates up to 1.5 per cent have been reported from Russia. During the same period of time the number of mild reactions (chill, mild rise of temperature) was about 5 per cent.

Reactions Following Transfusions of Refrigerated Blood

—Upon the institution of the blood bank at the Bryn Mawr Hospital it was noted that many transfusions were followed by reactions both immediate and delayed. Formation of minute clots in the refrigerated citrated blood was at first suspected as being the cause of such reactions. Such filaments or coagula had already been noted by a number of workers and filtration of blood advised. For filtration we employ four layers of 40 mesh gauze with the aid of gentle suction to accelerate the process. This procedure is carried out in a closed system and has no demonstrable effect on the fragility of the erythrocyte as will be discussed later.

The removal of these coagula however did not diminish

In the Bryn Mawr Hospital where a plasma repository had been in operation for several years preservation of blood for the purpose of transfusion was established in January 1938 after a preliminary trial series to establish a proper technique

Method of Preservation

Briefly the blood is mixed with 4 per cent dihydric sodium citrate solution in 0.85 per cent saline in a ratio of 50 cc to each 500 cc of blood and preserved in hermetically sealed cylindrical n.c. glass bottles at a temperature of 2° C until the time of use. For the preparation of the solutions and glassware care is taken for the avoidance of contamination with pyrogens. The various operations are performed by the same group of trained laboratory workers.

Time Limit of Preservation

As the limit permissible for blood preservation we set at first the appearance of hemolysis which accorded with the opinion of most workers prior to 1938. Concerning the time of preservation there is a considerable variety of opinions some favoring shorter limits thus for blood preserved in saline citrate solution Lindenbaum and Stroikova advised twelve days and Doepp ten days. Others set the time limit of blood preservation at much higher figures. For example Jeanneney and Vieroze set the limit at twenty days. Gnoinski used blood sixty six seventy five and eighty five days old and Grozdoff states that the results obtained from a transfusion of blood which was preserved for a considerable length of time (over fifteen days) differ very little from the results of blood preserved for a more limited period of time. However little or no evidence is given in most of these reports to justify the conclusions.

Later Fantus and Shurmer and others advised limiting the preservation of refrigerated blood to ten days although in some hospitals the limit of preservation of citrated blood is still longer. In many reports the limits of blood preservation are set somewhat arbitrarily or at least without mentioning the rationale of the proposed period.

hemolysis beginning at 0.60 or more and complete hemolysis at 0.36 or more. The experiment was repeated on a similar series of five blood samples with comparable results.

Fragility tests were also done with every lot of blood used for transfusion for a period of several months during which over 100 samples were tested. An increase in the fragility of the erythrocytes under the conditions mentioned appears to

FRAGILITY OF CITRATED ERYTHROCYTES

NaCl %

AT 2°C

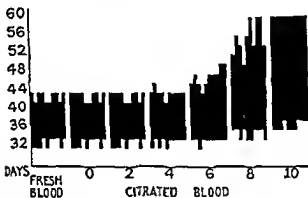


Fig 524 The fragility of erythrocytes of citrated blood (See text)

be a constant phenomenon after the fifth or sixth day of preservation.

Spontaneous Hemolysis

The time of occurrence of spontaneous hemolysis in a specimen of citrated refrigerated blood varies a great deal with the method used for the detection of hemolysis.

If we take as evidence of hemolysis the discoloration of plasma immediately above the layer of sedimented erythrocytes in an *undisturbed* specimen of citrated blood hemolysis is usually noted from the fifteenth to the twenty-first day, seldom later, occasionally before. If however hemolysis

the number nor alter the nature of the post transfusion reactions. These reactions consisted of chill and mild temperature elevation, jaundice, passage of dark colored urines. In more severe reactions there were pain over the bladder and in the lumbar region, nausea, vomiting and oliguria.

It was also observed that in patients receiving refrigerated preserved blood the rise in the erythrocyte count and hemoglobin content was not constant and often considerably below the average obtained by the use of fresh citrated blood in similar cases.

It appeared desirable to study systematically not only certain physical changes occurring in the citrated blood *in vitro* but also the fate of the transfused blood in relation to the period of preservation and to the conditions of the recipient. The purpose of the studies was to determine insofar as possible the usefulness and safety of refrigerated blood. The preliminary results were presented in the fall of 1939 at the meeting of the Pennsylvania State Medical Society in Pittsburgh. The observations and results will be summarized here.

PHYSICAL CHANGES OCCURRING IN CITRATED REFRIGERATED BLOOD

Fragility of Erythrocytes

Under the standardized conditions mentioned previously the fragility of erythrocytes to hypotonic solutions of sodium chloride was determined on ten specimens of blood from healthy donors. The fragility was determined before and after the addition of sodium citrate. Afterward each of the specimens was divided in ten aliquots and determinations were made daily on each one thereafter. These aliquots were preserved in cylindrical bottles similar in shape to the containers used for the preservation of larger specimens and of such size that the ratio between the volume of the specimen and the interfacies (air-plasma and plasma-packed erythrocytes) was comparable. The results are illustrated graphically in Fig. 5-4. There is practically no change during the first four days but with the sixth day the fragility is increased in every sample tested. By the tenth day all samples show

hemolysis beginning at 0.60 or more and complete hemolysis at 0.36 or more. The experiment was repeated on a similar series of five blood samples with comparable results.

Fragility tests were also done with every lot of blood used for transfusion for a period of several months during which over 100 samples were tested. An increase in the fragility of the erythrocytes under the conditions mentioned appears to

FRAGILITY OF CITRATED ERYTHROCYTES

NaCl % AT 2°C

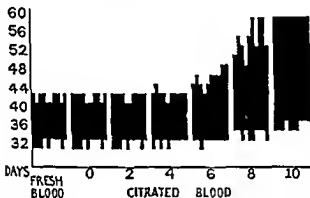


Fig. 4.—The fragility of erythrocytes of citrated blood (See text) during the period of storage.

be a constant phenomenon after the fifth or sixth day of preservation.

Spontaneous Hemolysis

The time of occurrence of spontaneous hemolysis in a specimen of citrated refrigerated blood varies a great deal with the method used for the detection of hemolysis.

If we take as evidence of hemolysis the discoloration of plasma immediately above the layer of sedimented erythrocytes in an *undisturbed* specimen of citrated blood, hemolysis is usually noted from the fifteenth to the twenty-first day, seldom later, occasionally before. If, however, hemolysis

ysis is determined after gently mixing the blood as it would be done before transfusion and allowing the erythrocytes to settle again by gravity. Considerable hemolysis can be detected much sooner usually between the tenth and the fourteenth day. Centrifugation of the blood for the purpose of determining the presence of hemolysis is desirable and does not appear to cause damage unless the blood has been preserved too long.

From these simple observations it appears that judgment of the state of preservation from the appearance of hemolysis of an undisturbed specimen of blood is not a safe procedure unless we accept the conclusion of Gryninski and Grozdoff that the presence of hemolysis is not a contraindication to the use of blood. The question of the danger involved by the intravenous administration of hemolyzed blood is an extremely controversial one. While it is true that even relatively large amounts of purified or crystalline hemoglobin solution can be safely administered intravenously, whole hemolyzed blood does not appear to be a safe material for intravenous use.

In conclusion, even if in the largest majority of cases the intravenous injection of a limited amount of hemolyzed blood is not followed by a permanent demonstrable renal damage, it is likely that damaged erythrocytes will last but a short time in the recipient's circulation, thus defeating the purpose of a whole blood transfusion. This is clearly demonstrated by the in vivo observations which follow.

Effect of Shaking and Filtration on the Fragility of Erythrocytes

Fragility studies were carried out on fifteen blood samples before and after gentle shaking (to obtain a complete mixture) and filtration as practiced on all specimens before transfusion. Results are summarized in Table 1. Similar studies were also carried out on ten lots of blood divided immediately after collection in five aliquots and kept up to ten days. Each day, beginning with the sixth, one lot was tested for fragility before and after mixing and filtration.

Under the experimental conditions, gentle shaking and filtration of blood preserved not more than ten days does not

TABLE 1

F C T P (S l o l t
 l v l t vt

Lot	M C	I	D J t	R g f H m ly		th Hypot	S h S c l t	
				H f I H t	S k k I t		A f I H t	S k k I t
104	111		1	42	32		42	32
245	1V		1	42	34		42	34
256	1V		1	42	32		42	34
168	1I		2	42	32		42	32
244	1V		2	41	32		41	32
246	1V		3	42	36		42	36
250	1V		3	41	32		41	32
251	1V		3	42	32		42	32
261	1V		3	41	32		44	32
272	1V		3	44	32		44	34
166	1I		4	42	32		44	34
249	1V		4	44	34		41	34
101	111		4	42	32		42	34
243	1V		4	44	34		44	34
101	1I		5	42	32		42	32

TABLE 2

1 CT (S 1 1

1 6 312 M 6 1 18

Day	Left		Right	
	Stalks	Heads	Stalks	Heads
6	44	36	44	36
7	48	36	50	36
8	48	38	50	38
9	56	38	57	38
10	60	41	60	41

Lot 114 Met C 1 IV

6	42	32	42	32
7	44	32	44	32
8	46	34	48	34
9	50	36	50	36
10	60	38	60	40

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Under the experimental conditions gentle shaking and filtration of blood preserved not more than ten days does not

TABLE 1

EFFECT OF STORAGE IN THE FREEZER ON THE FATE OF

Lot	Mos Group	Days of Preservation	Regimenly		th Hypot		Sh Sh t	
			B f	Sh k g d I h t	Aft	Sh k g d F l t		
104	III	1		42 32		42 32		
24	IV	1		4 34		4 34		
256	IV	1		42 32		42 34		
168	II	2		4 32		4 32		
244	IV	2		44- 32		44- 3		
246	IV	3		4 36		42 36		
250	IV	3		44- 3		44- 32		
251	IV	3		42 3		42 3		
261	IV	3		44 32		44- 32		
272	IV	3		44- 32		44- 34		
166	II	4		42 3		44- 34		
248	IV	4		44- 34		44- 34		
101	III	4		42 32		42 34		
243	IV	4		44- 34		44- 34		
104	II	5		4 3		42 3		

TABLE 2

FATE OF STORAGE IN THE FREEZER ON THE FATE OF

Lot 312 M G p IV

Days of Preservation	Regimenly		th Hypot		Sh Sh t	
	B f	Sh k g d F l t	Aft	Sh k g d F l t		
6		44- 36		44- 36		
7		48- 36		50- 36		
8		48- 38		50- 38		
9		56- 38		56- 38		
10		60- 44		60- 44		

Lot 314 M G p IV

6	42 32	42 32
7	44- 32	44- 32
8	46- 34	48- 34
9	50- 36	50- 36
10	60- 38	60- 40

appear to cause an appreciable increase in the fragility of the erythrocytes (Table)

Similar experiments carried out on blood specimens older than ten days and occasionally even on specimens nine and ten days old show that mixing and filtration cause an appre-

E 0 17 7 910 2
t 100 60 5 0 1.0

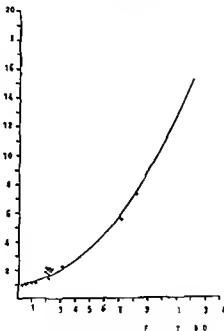


Fig 55-R1 ash p f h e f extra d blood d h h m gl l
ci f perm pl sm Th plasm w b d b ce trf ga
f ra d bl w d + C d m d d rbf f
h f collec

cible increase in the fragility of erythrocytes. As stated before specimens ten to fifteen days old will as a rule show spontaneous hemolysis following gentle shaking to obtain a complete mixing of cells. By gentle shaking is meant in all cases a rotating motion sufficient to carry in an even suspension the sedimented erythrocytes.

With more vigorous shaking or shaking repeated daily the effect on the fragility of the erythrocytes is proportionately more severe. It is to be noted that with blood less than five days old it requires a considerable amount of shaking to increase sensibly the hemolysis and fragility of the erythrocytes but citrated blood preserved over seven days shows considerable hemolysis after violent shaking.

The estimation of hemoglobin by simple observation is extremely difficult and unreliable. For the estimation of the hemoglobin in plasma we have employed for some time Chornock and Karr's²⁸ modification of the visual benzidine method of Letonoff which appears to be sensitive to about 0.5 mg of hemoglobin. Results obtained by this method in citrated refrigerated blood maintained at C are shown graphically in Fig. 575.

THE FATE OF TRANSFUSED REFRIGERATED BLOOD

Ag f Bl d Hyp bl b em d J d e

Blood bilirubin determinations together with clinical observations were made before and after transfusion in seventy-seven cases. In addition the fragility of the transfused erythrocytes was determined in each instance as well as the daily variations in the erythrocyte count and the hemoglobin content of the blood in all the patients.

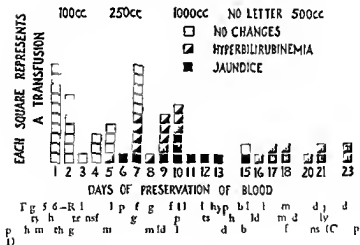
Sixty-three transfusions were given to patients suffering chiefly from mild to moderately severe posthemorrhagic anemias or mild chronic and subacute infections. They will be considered as Group 1. None of the patients in Group 1 showed very severe anemias or evidence of increased blood destruction. In all the cases of Group 1 the bilirubin content of blood serum was normal before the transfusion (0.5 mg or less per 100 cc). In forty-seven of these cases the bilirubin determinations were made before transfusion and from twelve to eighteen hours after; in the remaining sixteen cases bilirubin determinations were made before transfusion and at various intervals after up to forty-eight hours. The fourteen transfusions considered under Group were given to nine patients showing before transfusion hyperbilirubinemia of

various origin and severity. This group will be discussed separately.

Group I

The relationship of the age of blood hyperbilirubinemia and jaundice in the first group is shown in Fig. 5. It will be noted that in twenty-five transfusions with blood five days old or less there was only one case (4 per cent) of hyperbilirubinemia, a mild one, and only two cases (8 per cent) of mild chill and mild thermic reaction. One occurred in a

AGE OF BLOOD, HYPERBILIRUBINEMIA AND JAUNDICE

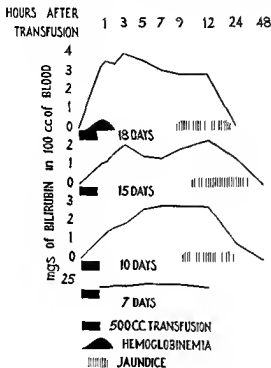


patient convalescing from optic atrophy and the other in a patient with chronic atrophic arthritis.

In the remaining thirty-eight cases in which blood six to twenty-three days old was used hyperbilirubinemia occurred in thirty-two cases or 84 per cent. Hyperbilirubinemia occurred in all but one patient receiving blood eight days old or more. The one exception was a case of epistaxis hemorrhage in which the blood transfusion of fifteen-day-old blood was stopped because of chill when only 100 cc had been given. Of these thirty-eight cases twelve (31 per cent)

had chill and/or temperature elevation following the transfusion and thirteen (34 per cent) had jaundice

Jaundice following transfusion of preserved blood has been reported it is likely that these reports are limited to the more severe cases of jaundice The jaundice is usually light and



F g f 7 - G p l h g h l h p f h g f b l d d h
f f d d g f h l rub m f h m g l b m ft

of short duration in patients receiving transfusions in the late afternoon it is usually not visible by the next day. Unless therefore the patients are carefully observed at regular close intervals the jaundice may in the majority of cases pass unnoticed

The jaundice usually reaches the peak eight to ten hours

after transfusion occasionally before it is seldom visible after twenty four hours. Except in severe cases it can be detected only in the sclerae. In a few cases the jaundice is more severe being readily observed in both sclerae and lasting up to forty eight hours. It has often been noted that in the most severe cases of jaundice there is an actual drop in the total erythrocyte count following transfusion (see Fig. 529).

The rise of bilirubin in the blood is very rapid (Fig. 527) and the serum bilirubin content often over 3 mg. per 100 cc. Similar findings have been reported by DeGowin⁴⁴ in post transfusion reaction. Increase in the bilirubin content is often present as early as a half hour after the beginning of the transfusion. During the transfusion and for a period of half to one hour after hemoglobinemia is also present. Bilirubinemia and jaundice are influenced not only by the age of the blood but naturally also by the size of the transfusion. This is particularly true of jaundice.

The *speed factor* has not been investigated in all transfusions the average speed was 4 cc. per minute the maximum rate 5 to 6 cc. per minute. In all cases of bilirubinemia the Van den Berg test gave a positive indirect reaction.

Fragility of Erythrocytes and Hyperbilirubinemia

Figure 528 shows the close parallelism between fragility of erythrocytes used in the transfusion and the incidence of hyperbilirubinemia in Group 1. Of twenty five transfusions employing blood with a normal fragility to hypotonic salt solution none was followed by hyperbilirubinemia. Of twenty five transfusions employing blood with hemolysis beginning at 0.6 per cent of sodium chloride or over twenty four (96 per cent) showed hyperbilirubinemia. The lone exception received only 100 cc. of blood. The fragility tests were done as a rule after the blood had been mixed but before filtration.

There appears to be therefore a close relationship between the age of blood the fragility of the erythrocytes and the incidence of hyperbilirubinemia and jaundice. This does not imply that decreased resistance to hypotonic solutions is the only factor involved in the accelerated destruction of the

transfused erythrocytes and the resulting hyperbilirubinemia. The fragility of the erythrocytes employed in the transfu-

FRAGILITY OF ERYTHROCYTES AND HYPERBILIRUBINEMIA

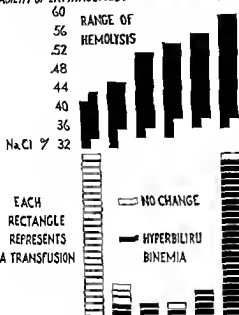


Fig 328-R1 hp ff gal ty f yth yt p dhp bl rub m
vry th r f ns (G p l)

sion however appears to be a very reliable index of their state of preservation

§ p 2

According to the mechanism of the hyperbilirubinemia present before the transfusions the nine cases of Group 2 will be divided into three subgroups as follows

(a) *Hyperbilirubinemia due to accelerated blood destruction from an increased and/or altered activity of the elements normally breaking down old erythrocytes* This group is represented by two cases of pernicious anemia with three transfusions. After each transfusion there was an increase of

the already existing hyperbilirubinemia regardless of the age of blood (one to seven days old) Hyperbilirubinemia following transfusion of fresh citrated blood in patients of pernicious anemia has been observed by me in a certain number of patients. It appears to be more common when large quantities of blood (500 cc) are employed in the transfusion.

(b) *Hyperbilirubinemia due to accelerated blood destruction from a lowered resistance of the erythrocytes to presumably normal activity of the elements breaking down old erythrocytes* and hyperbilirubinemia accompanying severe infection. This group is represented by a case of sickle cell anemia with two transfusions, one case of staphylococcal pneumonia, two cases of *Streptococcus viridans* endocarditis, one case of chronic lymphatic leukemia, one case of peritonitis. In the transfusions with blood less than five days old (six transfusions) there was no increase of the pre-existing hyperbilirubinemia; with blood over five days old there was a sharp increase. In other words, this subgroup acted like subgroup *a* as would be expected.

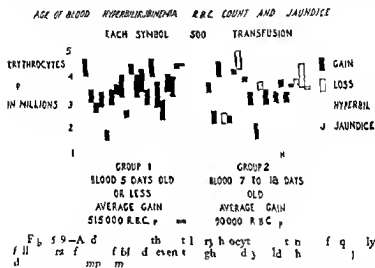
(c) *Hyperbilirubinemia due to liver diseases*. This group is represented by a case of biliary cirrhosis with four transfusions. There was a sharp rise in the serum content of bilirubin and a deepening of jaundice after each transfusion, the blood used being two to four days old.

Th Eff + f T f f R f g t d Bl d th Eryth yf
C +

We have already noted that transfusions of refrigerated blood were often not followed by the expected rise in the erythrocyte count and the hemoglobin content. In this study will be considered only those cases in which at the time of transfusion there was no severe bleeding or obvious alteration of the water balance and in which the erythrocyte count and the hemoglobin content did not show conspicuous fluctuations in the days preceding the transfusions. Pellegrini has pointed out how difficult it is to evaluate the variations of the erythrocyte count and the hemoglobin percentage following transfusion because of interchanges between tissues and blood. The figures given in this study must therefore

be considered mostly as comparative data and the results more suggestive than conclusive

Erythrocyte counts were made twenty four hours or less before transfusions usually immediately before and between twenty four and forty eight hours after transfusion. All the blood counts as well as the bilirubin estimations were made by the same technician with standardized pipettes and technic. All patients were adults and all received 500 cc of blood. In Group 1 (twenty cases) the blood was less than five days old and none of the patients showed increase of



the bilirubin content of the blood after transfusion. In Group 2 (nineteen cases) the blood was seven to eighteen days old (mostly between seven and ten days old) all patients showed hyperbilirubinemia after transfusions. Figure 529 illustrates graphically the findings. In the twenty cases of Group 1 the average gain in the erythrocyte count following transfusion was 515 000 per cu mm. No patient of this group showed a decline in the erythrocyte count following transfusion.

In the nineteen cases of Group 2 the average gain in the erythrocyte count following transfusion was 90 000 per cu mm or less than one fifth of the average gain showed by

patients of Group 1. In seven cases transfusion was followed by a decline in the erythrocyte count.

In addition to hyperbilirubinemia twelve cases of Group 2 also showed jaundice. In the seven cases showing a drop in the erythrocyte count following transfusion jaundice was present in all but one.

Failure in the expected rise in the erythrocyte count following transfusion of certain lots of blood (seven days old or more) in patients not showing at the time of transfusion considerable blood losses nor excessive blood destruction suggests the probability that *a large portion of the transfused blood is rapidly destroyed and eliminated*.

Another consideration that leads to the same conclusion is the finding of large amounts of hemoglobin in the blood of a number of patients receiving transfusions of preserved blood. In several observations in patients immediately following transfusion of blood from seven to eighteen days old it has been found that the hemoglobin concentration in the plasma may be as high as 0.53 per cent. In a specific instance a woman aged twenty-eight years suffering from a moderate posthemorrhagic anemia (3,100,000 erythrocytes per cu mm) was given a transfusion of 500 cc of eighteen-day-old blood. This did not show gross signs of hemolysis *in vitro*. One-half hour after completion of the transfusion the oxalated plasma contained 0.44 per cent of hemoglobin. On the basis of the body weight the patient's blood mass was estimated roughly at 4500 cc. The patient's blood having an erythrocyte volume of 75 per cent the total quantity of plasma was estimated at approximately 3375 cc. Therefore the circulating blood of the patient one-half hour after transfusion contained approximately 18 gm of free hemoglobin. The hemoglobin content of the transfused blood being 14 gm per cent we may assume that 150 cc of blood had undergone hemolysis within one-half hour of completion of the transfusion. This patient had a serum bilirubin content of 4.1 mg per 100 cc three hours after the conclusion of the transfusion. There was no chill or other immediate complaint but in about nine hours the patient became jaundiced (see Fig 527).

In another instance a male aged twenty three years who had recently undergone a colostomy was given 500 cc of ten day old blood. One half hour after completion of the transfusion the oxalated plasma contained 0.53 per cent of free hemoglobin. Seven hours later the serum bilirubin was 3 mg per 100 cc. The patient had a febrile reaction and became jaundiced. Before transfusion the patient had 4 610 000 erythrocytes per cu mm. four hours after they were 3 770 000.

The destruction of a large number of transfused erythrocytes when the citrated blood was preserved more than seven days was confirmed by the sharp increase in the total bilinogen output in the days following the transfusion. In one patient who received 500 cc of ten day old blood the bilinogen output from a normal of 95 mg for the twenty four hours before the transfusion rose to 400 mg for the twenty four hours following transfusion. A quantitative relationship between the age of the blood, size of transfusion and bilinogen output was attempted but the data are insufficient to warrant detailed analysis and conclusions.

P t f L k yt d Pl telets

The survival of leukocytes and platelets has been dealt with in a number of reports. However estimation of survival of these cells has been often based on the consideration of the number in the preserved blood without much consideration given to the state of preservation and the consequent physiological activity. Thus neutrophils appear to remain in the refrigerated blood for several days. However after a few hours of contact with the sodium citrate solution we have found that locomotion and phagocytosis of neutrophils are impaired. Phagocytic power of neutrophils may be to a certain extent restored if the cells are carefully washed. It is possible that after transfusion of citrated blood and elimination of sodium citrate the phagocytic activity may be partly at least regained. Shamov found that phagocytosis is fairly well preserved in cadaver blood for the first eleven hours after death. Karavanov found that polymorphonuclears of preserved citrated blood preserve some of their phagocytic

activity until the fifth or sixth day but that phagocytic power declines sharply after the second day. To demonstrate phagocytosis it was necessary to wash the leukocytes carefully to remove sodium citrate. Therefore it is likely that *the time of useful survival of leukocytes in citrated refrigerated blood is very short*.

Platelets survive in citrated refrigerated blood for a short time. Drew and Scudder found that the platelet count falls to less than 100,000 in twenty-four hours and to about 40,000 in three days. We found that in addition to rapid disappearance from the citrated blood the platelets show severe degenerative changes within a few hours of collection of the blood. Similar findings are reported by Kolmer. Howarth and Skinner found that phagocytic activity for several pathogenic bacteria is reduced in seventy-two hours of preservation.

The problems of the preservation of prothrombin complement and specific antibodies have been reported elsewhere and will be omitted here.

ADDITION OF ISOTONIC GLUCOSE SOLUTION TO CITRATED BLOOD

The solution employed by Rous and Turner in 1916 is a much better preservative for blood than plain citrate. Its practical use, however, is limited because of (1) the excessively large bulk of the resulting mixture and (2) the high concentration of sodium citrate necessitating the removal of at least part of plasma and resuspension of the red cells in saline solution or Locke fluid.

The addition of glucose to sodium citrate was revived in 1936 by Perry, who used a dextrose-lithium citrate mixture later on by many others including DeGowin et al., Maizel and Whitaker, and Belk.²⁸ The conclusion is that the addition of large quantities of isotonic dextrose solution to blood slows considerably the rate of hemolysis, as compared with that of blood preserved in plain sodium citrate solution. DeGowin recommends a mixture of 10 volumes of blood, 13 volumes of 3.4 per cent anhydrous dextrose and 1 volume of 3 per cent dihydric sodium citrate in water. Belk uses a mixture of 4 parts of blood and 1 of glucose solution.

The preservation of erythrocytes is definitely better when maximal quantities of isotonic glucose are used. The limit of useful storage of blood preserved in solution rich in glucose has been variously placed at three to four weeks.

It may be conservatively stated that the addition of sufficiently large quantities of isotonic glucose solution to whole blood when properly done will increase the useful period of erythrocyte preservation to about three weeks or three times as long as the expected period of preservation of erythrocytes in plain sodium citrate solution.

This improved preservation is proved by studies of the resistance of the erythrocytes to hypotonic salt solution and to shaking. It is also proved by *in vivo* studies of the serum bilirubin content of the recipient's blood after transfusion at least when the amount of transfused whole blood does not exceed 500 cc.

Similar conclusions were reached by Belk from studies of the survival of erythrocytes in the circulating blood of the recipient by the method of Ashby. The addition of glucose solution has no appreciable effect on the preservation of leukocytes or platelets.

THE PROBLEM OF BLOOD BANKS

Factors militating against Adoption of Blood Glucose Mixtures

It would appear from the foregoing that the solution of the problem of blood banks rests simply upon the employment of a preserving fluid containing large quantities of isotonic glucose solution. This conclusion however is not entirely acceptable for many reasons which will be briefly reviewed.

1. The bulk of the transfusion fluid is large especially when the amount of whole blood required is more than 1 liter.

2. The dilution of the blood when maximal quantities of isotonic glucose solution are used interferes seriously with the effectiveness of the transfusion in cases of severe shock with widespread capillary damage in view of the fact that the resulting plasma protein concentration is greatly reduced. Thus with DeGowin's solution the average total plasma protein concentration of the blood citrate glucose mixture is but 3 gm. in 100 cc.

3 The addition of isotonic glucose solution to citrated blood slows but does not suppress the aging of erythrocytes stored at plus 4°C . It is to be expected that the longer the period of preservation the larger the number of erythrocytes which will be rapidly destroyed after transfusion. This becomes even more significant when large amounts of blood are transfused at any one time.

4 The addition of glucose solution makes the technic of blood collection somewhat more complicated as it is necessary to sterilize the solution of glucose and that of sodium citrate separately and mix them before the blood is collected under aseptic precautions.

5 In hospitals where the number of daily blood transfusions is large the need for preservation of blood for a period longer than five days is not urgent.

6 Preserved blood is not recommended for the treatment of infections and of certain hemorrhagic diseases.

Other reasons militating against the universal adoption of blood-glucose mixtures are to be found in the following paragraphs.

The Pros and Cons of the Red Cross Blood Bank

Blood banks were instituted and are maintained mainly (1) to take care of emergency whole blood transfusions (2) to simplify and better the transfusion service.

Whole blood transfusion appears justifiable as an *emergency* lifesaving procedure in but two conditions: (a) poisoning from substances which render hemoglobin incapable of carrying oxygen (such as carbon monoxide) (b) cases of severe hemorrhage with shock in which the hemorrhage continues at the time of treatment.

Concerning () the blood bank facilitates whole blood transfusion because of the regular hours in which blood may be collected so that trained laboratory technicians may attend to collection, typing and serologic studies in an orderly manner and with the best possible technic.

If one considers critically the record of the average hospital over a period of a year the cases of bona fide emer-

agencies requiring whole blood transfusions are relatively few. In our institution they are well below 5 per cent of the total amount of blood transfusions given in a year—that is less than twenty 500 cc. doses of blood a year.

The experience of many hospitals where plasma banks have been instituted has been a definite progressive decrease in the relative and/or absolute number of whole blood transfusions. Thus in the Bryn Mawr Hospital the percentage of blood donations used as whole blood for transfusions has decreased as shown in Table 3.

TABLE 3

D i c	W o B T 11 1938-1942		HE B M W		
	1938	1939	1940	1941	1942 (8 m th)
Blood d t T t l wh l blood	625	861	1184	1277	883
t n s P t wh l blood	530	567	427	446	286
transfus T talp u t d ys	84.8 62.243	6.8 63.62	36 66.227	34.9 71.086	32.3 51.845

It appears necessary therefore to integrate the function of the blood bank with the operation of plasma banks. Since undiluted plasma is easier to prepare and to use and of more uniform clinical effect in routine use it appears desirable to prepare it from plain citrated blood in which plasma dilution by anticoagulant has been kept down to a minimum. In other words it is recommended that instead of trying to prolong the expected life of transfused erythrocytes by the addition of large quantities of isotonic glucose solution to whole blood plain citrate solution be used for the preservation of blood. Moreover the use of preserved blood should be limited to five days. At the end of each week, all the unused blood is used for the preparation of plasma. This method is in use in many institutions and appears to work very satisfactorily. It offers the benefits of a blood bank combined with those of a plasma bank with the minimum outlay of

technical labor. This is true of large and medium sized hospitals.

Other considerations which have very important bearings on the question of blood banks are the *size of the institution* and the *type of prevailing practice*. Small hospitals and hospitals where the number of blood transfusions is relatively small do not profit by the institution of a blood bank. If a blood bank is instituted glucose containing solution should be used as preservative. For small hospitals the blood donor registry proposed by Pons appears admirably suited. Briefly, volunteer donors of the community served by the hospital are organized along the lines of volunteer firemen. Their blood is carefully typed and the donors are periodically checked. In case of need either for an emergency or otherwise several donors of suitable type are available immediately. In this type of institution blood plasma will take care adequately of most emergencies leaving only very few cases in which an emergency whole blood transfusion need be done.

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technical labor. This is true of large and medium sized hospitals.

Other considerations which have very important bearings on the question of blood banks are the *size of the institution* and the *type of prevailing practice*. Small hospitals and hospitals where the number of blood transfusions is relatively small do not profit by the institution of a blood bank. If a blood bank is instituted glucose containing solution should be used as preservative. For small hospitals the blood donor registry proposed by Pons appears admirably suited. Briefly, volunteer donors of the community served by the hospital are organized along the lines of volunteer firemen. Their blood is carefully typed and the donors are periodically checked. In case of need either for an emergency or otherwise several donors of suitable type are available immediately. In this type of institution blood plasma will take care adequately of most emergencies leaving only very few cases in which an emergency whole blood transfusion need be done.

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PLASMA AND SERUM AS BLOOD SUBSTITUTES

STUART MUDD M D †

d

EARL W FLOSDORF Ph D ‡

THE principal functions of the blood may be considered to be (1) oxygen and carbon dioxide transport functions with which the hemoglobin and carbonic anhydrase of the erythrocytes are concerned (2) the clotting function in which among others the proteins fibrinogen and prothrombin participate (3) the immune function in which the monocytes polymorphonuclear leukocytes complement and specific and nonspecific antibodies found chiefly in the γ globulin fraction participate (4) the osmotic control of water and electrolyte balance in the body and (5) the transport of nutritive substances waste products hormones and enzymes Problems involved in the transfusion of whole blood are outside the scope of this clinic

THE RATIONALE OF THE USE OF BLOOD SUBSTITUTES

The major interest which has developed recently in civil and in particular in military medicine regarding blood substitutes § centers about the emergency treatment of secondary shock and hence about the osmotic control of water

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tween the volume of blood and the volume capacity of the vascular stream bed. This disparity if not compensated causes circulatory deficiency.

In traumatic shock and hemorrhagic shock and burns *direct loss of fluid* from injured regions may lead to circulatory deficiency (Cannon.)

Compensation is accomplished through responses activated probably by impulses from the carotid sinus. Activity of the sympathoadrenal system causes constriction of peripheral arteries, the discharge of reservoir blood from the spleen into the systemic circulation and stimulation of the heart by sympathetic impulses in cooperation with the adrenal medullary hormone. So long as the mechanism of compensation is effective there is no marked decline in the blood pressure but the latter is maintained at the expense of volume flow to peripheral organs which is reduced markedly. This stage of shock can sometimes be recognized by the presence of hemoconcentration. A progressive decline in the blood pressure signifies that compensation is failing and that the end is near. It is a sign of departed opportunity.

Capillary atony in extensive areas reduces both the total and the effective blood volume and leads to a reduction of the volume flow. This reduces the delivery of oxygen to the tissues. When the supply of oxygen falls below physiologic limits it augments the capillary atony. Deficiency of oxygen below physiologic limits causes dilatation and hyperpermeability of capillary walls. This effect introduces a self-perpetuating quality which operates as a vicious circle and leads to irreversible changes.

Successful management of shock requires early recognition and effective measures for breaking the vicious circle. These will be directed toward removing the cause, toward increasing the blood volume and toward relieving anoxia.

The principal mechanisms which initiate this cycle of secondary shock may then be taken to be (1) the loss of blood and plasma into the injured area, (2) injury to capillary endothelium resulting in a leakage of plasma protein and fluids from circulation into tissue spaces and (3) the tissue anoxia which results from inadequate circulation whether brought

and electrolyte balance for the basic physiologic deficiency in shock is reduction of circulating fluid volume and the primary consideration in its treatment is prompt restoration of adequate circulating fluid volume

Secondary Shock

The main feature of present conceptions of shock is recognition of different varieties—hemorrhagic traumatic (with loss of blood into damaged tissues) burn shock (with loss of plasma through burned surfaces) and toxic (from infection or from poisons arising in dead or dying tissues). In all these conditions the central fact is a loss of blood volume below the minimal capacity of the system when the compensatory adjustments fail. In the first two types of shock mentioned above hemoconcentration does not occur primarily when the circulation fails or is failing the capillary count (dermal) is found high. In shock from burns hemoconcentration is routine as would be expected. In toxic shock hemoconcentration may be present early (Cannon).

Etiology—Secondary shock may result from extensive operations from the severe injuries of civil accidents or military wounds or from burns severe infections profound intoxications and other conditions. Loss of blood emotional stress prolonged exposure to cold and physical and nervous exhaustion may all be contributing factors. The cycle of deranged function that characterizes the shock state ultimately involves loss of fluid and plasma proteins through the endothelium and tissue anoxia (oxygen deficiency). Unless this vicious circle can be broken circulatory failure and death ensue. Mechanisms involved have been summarized by Moon as follows:

Endothelium is delicately sensitive to lack of oxygen to metabolic products cytoplasmic substance bacterial toxins and to a wide variety of chemicals and drugs. When affected by any such substances the endothelium becomes relaxed atonic and abnormally permeable to blood plasma. The sequestration of blood in dilated capillaries reduces the effective blood volume and the leakage of plasma into tissue spaces lowers the total blood volume. This creates a disparity be

mentioned as early criteria in each case however difficult of clinical application. Determination of the circulation time is suggested by Necheles and Levinson as a diagnostic criterion. Fall in blood pressure may occur so late in secondary shock as to be in Dr Moon's words a sign of departed opportunity.

Application of Heat—The studies of Blalock and Mason do not support the custom of applying heat vigorously in secondary shock unless steps are taken simultaneously to augment the reduced blood volume. No matter how shock is initiated the ultimate cause of deterioration is peripheral stagnant anoxia, i. e. lack of sufficient oxygen to maintain life in the cells of vital structures at ordinary temperatures. It is clear that two approaches to this dilemma may be made. The oxygen supply to the tissues can be increased to meet the existing demand or the demand for oxygen can be reduced to meet the existing supply. Hypothermia by lowering the rate of metabolism reduces the tissue requirement for oxygen. It might be said that means to elevate considerably the skin temperature of the patient in shock should be used with caution if at all. Much more important is the augmentation of the reduced blood volume by the introduction of whole blood or plasma after which warming is less apt to bring about an intolerable reduction in the effective volume of circulating blood.

Some confusion regarding the application of heat to patients in shock has no doubt resulted from insufficiently clear distinction between the physiological states and needs of patients in primary and in secondary shock. Following a severe injury so called primary shock frequently occurs. This is really a condition of vascular collapse in which the tone of the peripheral vessels is diminished reflexly as a result of nervous or psychic stimuli. The vascular bed is dilated to such an extent that the volume of blood becomes insufficient to maintain an adequate venous return to the heart and thus an adequate output to the periphery. It may be difficult to distinguish this form of collapse from true secondary shock therefore all patients admitted with a feeble pulse and lowered blood pressure should be treated immediately for

about by lowered blood pressure or by reflex vasoconstriction

The nature of the *injury to capillary endothelium* has been under active discussion since World War I the particular point at issue being whether or not a toxic product or products formed at and absorbed from the area of injury is responsible for the initial injury to endothelium. Experimental evidence which seems to the reviewer favorable to this hypothesis has been contributed by Cullen, Schechter, Freeman and Laws¹ these experimenters were able largely to control fluid loss into the site of injury by taping the limb which was subsequently injured in animals in which reflex vasoconstriction was prevented by an antecedent sympathectomy. Secondary shock nevertheless ensued. Solandt and Best were able in some but not all experiments to produce progressive circulatory failure in animals cross transfused with animals in shock. Moon has been able to produce secondary shock by means of sterile finely ground muscle pulp implanted in the peritoneal cavity. Crush injury or blood flow through a region long ischemic (leg) has demonstrated the reality of a toxic factor in these conditions (Cannon).

The long controversy regarding the existence or nonexistence of a product of injury toxic for endothelium seems then to the reviewer to be near agreement in the affirmative. Certainly no such satisfactory outcome can be claimed at present however for the attempts to establish the identity of such toxic product or products. Potassium has been suggested but the consensus seems to be that increased blood potassium is more probably a late result of tissue anoxia than an initiating cause of shock. Histamine or a histamine like substance have been suggested but without satisfactory evidence. Identification of this circulating product or products toxic for endothelium remains a central unsolved problem of shock.

Recognition of Incipient Shock—Another problem under active investigation and discussion is that of early recognition of incipient shock. Hemocoagulation as estimated from hematocrit or hemoglobin determination is recognized as a useful early sign of impending shock but is not invariable. Fall in muscle temperature and decreased plasma volume are

ratus¹ currently used for drying from the frozen state have been described under the terms *lyophile* *cryochem* *desivac* and *adtevac*. In each of these processes the plasma or serum is frozen and then desiccated in a vacuum at a rate sufficient to keep it frozen by the continued cooling incident to loss of latent heat of vaporization. The procedures differ essentially in the means used to remove the water vapor evaporated from the material undergoing desiccation. In the *lyophile* process the water vapor is condensed as ice in a bath kept cold by dry ice or by specially designed low temperature mechanical refrigeration in the *cryochem* process the water vapor forms a hydrate with Drierite a specially prepared regenerable calcium sulfate desiccant in the *desivac* procedure the water vapor is trapped in the oil of the large vacuum pumps used whence it is continuously separated by centrifugation or other specially designed vapor or steam ejector pumps are utilized in the *adtevac* process the water is absorbed on mechanically refrigerated silica gel. Desiccation may be carried out in the final containers or in bulk with subsequent transfer to final containers most operators prefer the former because of diminished risk of contamination and a greater ease of measuring and transferring liquid as compared with desiccated hygroscopic material.

Equipment is available on any scale from that for desiccation of a single container to that for plant scale production at the rate of many thousands of containers per week. For small scale operation the dry ice *lyophile* or *drierite* types of equipment are more economical the mechanically refrigerated *lyophile* the *desivac* and the *adtevac* equipment are all designed for larger scale operation.

Preservation in the frozen state can have advantages for hospital use. Where transportation is required particularly under adverse conditions desiccation from the frozen state has been accepted as the method of choice. In conditions where a hypertonic solution is required desiccation provides the means whereby the solids may be restored with an amount of water less than that of the original volume of plasma say one quarter or one third of the original volume.

Preservation in the frozen state utilizing equipment for

collapse. This treatment involves administering morphine if there is pain, getting the patient warm with blankets and sometimes hot fluids and putting the patient in shock position with the feet elevated because gravity plays such an important part in the pooling of blood. If the patient does not quickly improve under these conditions true secondary shock is probably present. (Janeway)

PRESERVATION OF PLASMA AND SERUM

Since the natural physiological correctives of shock are human blood plasma or serum it is appropriate to consider the forms in which plasma and serum are preserved and distributed for use.

Four general methods of preservation of plasma and serum may be discussed: (1) storage in the liquid state at refrigerator or room temperature with or without chemical preservative; (2) simple desiccation; (3) vacuum desiccation from the frozen state; (4) preservation in the frozen state.

Prolonged storage *in the liquid state* has the serious limitations: first that the various entities involved in the clotting and in the immune mechanisms undergo progressive deterioration and second that should any break in the sterile technique occur bacteria may survive and even multiply despite refrigeration and the presence of chemical preservatives. For short time storage or under conditions in which rigid asepsis can be assured, however, liquid storage offers obvious advantages. If stored plasma is to be injected intravenously, provision for first filtering out fibrin should be made.

Various techniques of *simple desiccation* have been described and tried out. In general it may be said that the plasma proteins are not completely protected by such procedures from alterations including denaturation of protein and reduction in solubility. Simple desiccation does not seem to offer enough in point of convenience to compensate for the deterioration in plasma proteins which occurs and such methods have found little application.

Vacuum desiccation from the frozen state and *preservation in the frozen state* are the methods of choice for prolonged preservation. Several types of procedures and appa-

lations are in each case specialized in ways appropriate to their special functions. In particular it has recently been pointed out by E. J. Cohn⁹ that *serum albumin* possesses distinctive properties which adapt it for the osmotic control of water and electrolyte balance in the body. Serum albumin has relatively great solubility and stability in solution; its solutions have relatively low viscosity; and molecules of albumin are of relatively symmetrical shape and charge distribution, small size and high net electrical charge. By special methods serum albumin may be purified and prepared in crystalline form.

Janeway and others have made considerable progress in the clinical evaluation of human serum albumin for the relief of shock. Results are extremely promising both as to efficacy and harmlessness. Evaluation of solutions of crystalline bovine albumin are also in progress. Questions of possible allergic and anaphylactic complications obviously require meticulous investigation with bovine albumin; progress thus far is reported as very encouraging.

Other substances under investigation as blood substitutes are autoclaved solutions of *pectin* which have been reported favorably by Hartman, Schelling, Harkins and Brush, on the basis of laboratory and clinical trial; a special preparation of gelatin called *isinglass* reported by Taylor and Waters; and gelatin prepared from bone collagen.

Although protein digests are not blood substitutes in the sense of serving for the immediate restoration of blood volume in the emergency treatment of shock, it is not unlikely that they may assume importance as supplements in the more prolonged treatment of hypoproteinemia, whether resulting from trauma or undernutrition. Whipple and his associates have reported that certain casein digests with average molecular weight of around 500 given to dogs by vein or subcutaneously are as effective as protein by mouth in building new plasma protein, and when protein cannot be eaten the digest can wholly replace food protein for many weeks. It may be that *casein digests* can be used with profit to supplement plasma injections or even to replace the intravenous plasma when the acute emergency is passed.

frozen foods has been particularly recommended by Strumia and by Elliott. Strumia regards the following technical points as essential: (1) fairly rapid freezing (freezing time not to exceed three to six hours) (2) maintenance in storage at a safe level below freezing (3) rapid thawing and warming to room temperature in the water bath at 37° C with occasional gentle agitation.

Electrophoretic patterns of plasma and serum which are delicately sensitive to alterations in concentration or physicochemical properties of the proteins are reported by Scudder¹ and by Curtis and Pembroke. The original patterns are unaltered by preservation in the frozen state or by desiccation from the frozen state; after simple desiccation the patterns are altered.

It is gratifying to realize that stores of blood substitutes in the form of vacuum dried plasma and frozen plasma were at hand even though not in adequate amount when the United States was first attacked and these served well at Pearl Harbor. It is also gratifying that the collection of human blood and preparation of blood substitutes has grown to enormous proportions: some 85,000 donations in Canada and some 375,000 donations to the Red Cross in the United States having been made up to June, 1941. The blood collected in Canada is being used to prepare serum vacuum dried from the frozen state (Best and Solandt) and that in the United States to prepare similarly vacuum dried plasma.

The importance of training medical officers and medical students in the pathologic physiology of shock, burns and hemorrhage and in the use of blood substitutes and blood transfusion has recently been emphasized. The procurement, processing and use of human blood plasma have been dealt with in great practical detail in a publication prepared under direction of the Subcommittee on Blood Substitutes of the National Research Council.

OTHER BLOOD SUBSTITUTES

Physicochemical studies of the proteins of the blood have shown that those in the several categories concerned respectively with respiration, clotting, immunity and osmotic re-

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EXPERIMENTAL AND CLINICAL EXPERIENCE WITH BLOOD SUBSTITUTES

The experimental and clinical experience reported by Medinger by Hill and Murhead by Strumia and McGraw Elliott and Marsh Kendrick and Newhouser Best Solandt and Ridout by Mahoney Kingsley and Howland by Necheles and Levinson by Self and Scudder and by others has established beyond question that both human plasma and serum are efficacious in the emergency treatment of shock and burns and in general in the correction of hypoproteinemic states. Either plasma or serum properly prepared and preserved may be used satisfactorily. The relative advantages of hypertonic versus isotonic plasma and serum have been much discussed.¹ An obvious indication for hypertonic plasma or serum is shock complicated by head injury with consequent cerebral edema increasing the osmotic pressure within the systemic circulation withdraws fluid from the central nervous system. Another special indication for hypertonic plasma or serum is in nephrosis as a diuretic (Aldrich and Boyle). In special conditions under which intravenous administration of blood substitutes is difficult injection into the marrow cavity of bones has been recommended.²

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CONTINUOUS SPINAL ANESTHESIA IN ABDOMINAL AND THORACIC SURGERY

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and

GEORGE W. PASCHAL, J. M.D.‡

CLINICAL OBSERVATIONS

SOME of the disadvantages of the single dose method of spinal anesthesia are (1) failure of the drug to take or produce anesthesia to the desired level or degree (2) the wearing off of the drug action before the operation is completed and (3) toxic symptoms or even sudden death following the intraspinal administration of a large dose of a toxic drug.

Since April 10, 1939, when we gave the first continuous or fractional spinal anesthetic, we have administered more than 7000 entirely satisfactory anesthetics by this method. In this clinic we are giving some of our observations and impressions in those cases.

We have used novocain (procaine hydrochloride) as the anesthetic agent. We believe this drug to be the least toxic of all drugs used in producing anesthesia by injection into the subarachnoid space. Laboratory investigation and clinical experience support this statement. Novocain is probably the shortest acting drug and lends itself well to the continuous method in which just sufficient dosage is used to produce anesthesia to the desired level and degree, the anesthesia being maintained as long as necessary by adding subsequent small

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fortable return trip to bed with a dry warm skin. The nurse has time to prepare a hypodermic of morphine and give it with the first complaints of pain. This may be helpful in reducing our incidence of respiratory complications.

Safety and *controllability* are the two things we desire most in spinal anesthesia. Sise has taught that the first thirty minutes of spinal anesthesia are the most dangerous. It is during this period that deaths and complications are most likely to occur and especially is this true when a single large dose of a toxic drug is administered. We believe that by giving much smaller initial doses of the drug its safety is enhanced. When the malleable needle is left in the subarachnoid space the drug can be rapidly recovered by withdrawing a sufficient quantity (5 to 15 cc.) of cerebrospinal fluid if unusual toxic symptoms develop especially in those patients who are very sensitive to the drug.

Our experience indicates that the *toxic symptoms* seen following injection of a drug into the subarachnoid space are not due to the drug that is fixed in the lipid elements of the sensory sympathetic and motor synapses producing anesthesia but are due to the absorption of the drug from the cerebrospinal fluid into the systemic (venous) circulation. (This factor will be further emphasized when we deal with spinal anesthesia used in thoracic surgery.) The respiratory center seems to be the most vulnerable to attack. The heart may stop first owing to direct action of the drug on the heart. When and if toxic symptoms of an alarming degree develop the first thing to do is to withdraw rapidly the cerebrospinal fluid containing the toxic agent. The greatest concentration of the drug is in the vicinity of the point of the needle. The nerves promptly recover from the anesthesia.

Spinal anesthesia is maintained by the drug that is present in the cerebrospinal fluid and when the concentration of this drug falls below a definite level the anesthesia promptly wears off. After anesthesia is established it takes relatively small doses to maintain it for any desired length of time. If we are doing serious technical operative procedures and it is important to maintain complete relaxation at all times we give an additional dose of 50 mg. of novocain (5 per cent)

doses as they are needed. The change in the method of spinal anesthesia from the single dose to the fractional dose technic now places spinal anesthesia in the same category with other anesthetics administered by the continuous or fractional dose method such as ether, cyclopropyl nitrous oxide and intravenous anesthetics.

We have found that *we can withdraw the drug from the subarachnoid space and take the patient awake rapidly from the anesthesia.* This observation was first made accidentally. Novocain (150 mg.) was introduced by the continuous method and at the end of five minutes anesthesia was found to extend to the sphincter process. Sterile drapes were applied to the abdomen and five minutes after testing the anesthesia an incision was made whereupon the patient screamed with pain and moved both legs. After the test of the anesthesia the syringe containing the unused novocain had been placed in a sterile folded towel but in so doing the anesthetist had inadvertently turned the stopcock thereby allowing the cerebrospinal fluid containing the novocain to flow from the subarachnoid space back into the syringe. When the difficulty was detected the plunger of the 10-cc. syringe was just ready to be forced from the barrel of the syringe. The plunger was returned promptly to its original markings, the anesthesia was promptly reestablished and the operation was performed under entirely satisfactory anesthesia.

For many months we made use of this observation. About fifteen to twenty minutes before the estimated termination of the operation we would slowly withdraw (usually by opening the stopcock) 5 cc. to 15 cc. of cerebrospinal fluid. Many of the patients were able to move their legs and help themselves from the operating table to the carrier when the operation was completed and the dressings applied. But we found that they were suffering pain, sweating profusely and complaining bitterly before the nurses could return them to bed. This was very undesirable particularly when traveling by stretcher on elevators and through halls of the hospital.

Now, instead of withdrawing the drug by removing cerebrospinal fluid, we usually give about 50 mg. of novocain at the completion of the operation to insure the patient a com-

of this size. We have had anesthesia with 50 mg. of novocain last for an operation that required one hour and forty five minutes.

After the initial injection of novocain subsequent injections of 50 mg. each generally are effective for approximately thirty minutes producing both motor relaxation and sensory block. By injecting small doses of novocain (15 to 20 mg.) into the subarachnoid space we have been able to produce sensory block (anesthesia) without causing motor paralysis. In the case of an elderly woman with a strangulated hernia we produced satisfactory anesthesia with 30 mg. of novocain.

We are of the opinion that by using the continuous method of anesthesia it is possible to lower the morbidity and mortality rates especially in serious and prolonged surgical procedures.

INDICATIONS

Continuous spinal anesthesia by the technic to be described has been used successfully by us in a wide variety of operations on the thorax, upper and lower abdomen and sympathetic nerves in urologic and gynecologic surgery, obstetrics and surgery of the extremities. It has been found to be safe and controllable and supplementary anesthetics are not needed.

In our series approximately 100 operations were above the respiratory diaphragm while 1900 were below it. A few sympathectomies consisting of the removal of the thoracic and lumbar ganglia required anesthesia above and below the diaphragm. We are entirely satisfied with this anesthesia for all closed chest operations. If the patients cough or have respiratory difficulty we change to intratracheal cyclopropane anesthesia. In one case it was necessary to change to cyclopropane. The two anesthetics may be combined in some instances. We have used continuous spinal anesthesia in practically all of our operations on the breast during the past eight months as for the removal of tumors, biopsies, simple mastectomies and radical mastectomies. There is much less bleeding, less shock and less renal irritation than when other methods of anesthesia are used. The convalescence is improved and shortened.

solution every thirty minutes. Otherwise we wait for the initial or previous dose to show signs of wearing off before we give an additional injection.

With one exception in our series anesthesia was produced to the desired level and degree and the operation was completed under spinal anesthesia. The exception here referred to was a case in which the right middle and lower lobes of the lung were being removed for bronchogenic carcinoma and while sensory anesthesia was present up to the level of the hyoid bone a persistent cough induced by the incidental tugging on the bronchus could not be controlled. In this instance cyclopropane was used for this part of the operation. In no other case was a supplementary anesthetic necessary. There were no anesthetic fatalities and no neurological complications. Toxic symptoms were promptly controlled by withdrawal of the drug by rapid aspiration of spinal fluid (3 to 15 cc) and by giving inhalations of oxygen.

As mentioned, novocain because of its shorter action and greater safety has been the drug of choice for producing spinal anesthesia by the continuous technique. Other drugs which have a more prolonged action are also found to be more toxic. There is no reason, however, why any drug or combination of drugs used in producing spinal anesthesia can not be used by the fractional dose, serial injection or continuous method. They should be safer when administered by this method than by the single dose technique since the patient is exposed to smaller amounts of the drug and because the drug can be recovered by aspiration of a sufficient amount of spinal fluid containing it should alarming symptoms develop and make this action necessary.

We have found that novocain produces anesthesia promptly when introduced in sufficient quantity into the subarachnoid space of the spinal cord. It takes approximately ninety seconds to relieve pain completely and produce muscular relaxation when it is given in subsequent injections. We feel that each patient is a case unto himself and that each has an individual response to novocain. We have observed an instance in which the anesthetic action of novocain disappeared fifteen minutes after a 100 mg. dose and subsequently after additional doses

EQUIPMENT AND ADMINISTRATION

Figure 530 illustrates and describes in detail the equipment for continuous spinal anesthesia

The patient is placed on a specially designed mattress and a very flexible special alloy lumbar puncture needle is inserted into the subarachnoid space where it remains during the operation. This needle is connected to a syringe by means of a 30-inch piece of rubber tubing (thick walled and small caliber) which is provided with Luer Lok connections at both ends.

The rubber covered mattress (Fig 530 VI a) has a cut out area 7 inches in length that comes under the lumbar spine when the patient is supine. There is a break in the center of the mattress so that the part which supports the legs may be detached for perineal operations. Provision has also been made to break the lower part of the mattress to allow the feet to be dropped when deep Trendelenburg position is desired (Fig 530 II and VI a 2 3). If an abdominal operation follows the perineal operation the patient may be pulled back into position and the lower half of the mattress replaced and made secure with straps and buckles (Fig 530 VI a 1).

The spinal puncture is made with the patient in the left lateral decubitus position so that his back is toward the side of the mattress with the gap in it. The malleable special alloy needles are made in three sizes 17, 18 and 19 gauge. We prefer 18 gauge needles. The site selected for spinal puncture depends upon the site of operation—the second or third for upper abdominal procedures, the third or fourth for lower abdominal operations, and the fourth or fifth for operations on the perineum, rectum and lower extremities.

A Sise introducer is used to puncture the skin. On with

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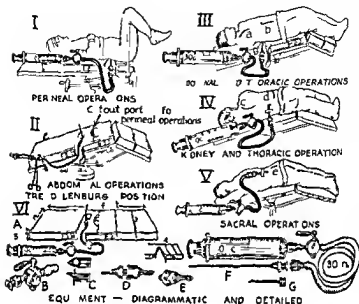


Fig. 530—Equipment for operations

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patient complains of abdominal discomfort or pain. Just as we would add more ether under similar circumstances to produce relaxation during inhalation anesthesia when this occurs during continuous spinal anesthesia we give a small additional dose of novocain usually 50 mg. We have noted that it takes approximately ninety seconds for this added dose to exert its full effect. We now give these additional doses in longer operative procedures at fairly regular anticipated intervals (usually every thirty to forty minutes) and are provided with uninterrupted ideal operating conditions throughout the operation.

PREOPERATIVE MEDICATION

We consider the preoperative medication to be of great importance. On the evening before the operation the patient receives 3 grains of nembutal by mouth. Three hours before operation the patient is given a second dose of 3 grains of nembutal. One hour before operation a hypodermic of $\frac{1}{4}$ grain morphine and $\frac{1}{100}$ grain of scopolamine is given. If the sedation is not sufficient $\frac{1}{8}$ grain of morphine is given intravenously or hypodermically as often as is necessary during the operation. By using proper sedation the patients are spared the unpleasant memories sometimes accompanying such an experience. Most of them sleep throughout the operative period and afterward for many hours.

COMPLICATIONS

During long and difficult procedures an intravenous injection of 10 per cent glucose solution is given via a vein in the leg. These patients also receive a blood transfusion at the end of operation if it is indicated. We make an effort to prevent and combat shock rather than wait until its onset before treatment is begun.

The blood pressure is controlled mainly by control of the dosage of the drug. By giving a small initial dose and adding subsequent small doses as needed marked drops in blood pressure are prevented.

The reason for the occurrence of *headache* following spinal anesthesia remains obscure. We have had this complaint

drawal it leaves a track for the soft malleable special alloy needle to traverse. When the cerebrospinal fluid escapes from the hub of the needle a 10-cc Luer Lok syringe is connected with it and enough fluid is withdrawn to make up a 5 per cent solution. Novocain is dispensed in 300- and 500 m ampules. For estimated short operations we use 300 m of novocain dissolved in 6 cc of cerebrospinal fluid and for long operations we dissolve 500 mg of novocain in 10 cc of spinal fluid making a 5 per cent solution in either case which contains 50 mg per cubic centimeter.

The syringe is disconnected and the needle is plugged by a Luer Lok plug to prevent the loss of spinal fluid. The syringe with the stopcock attached is connected to one end of the 30 inches of thick walled small bore rubber tubing. The stopcock is opened and 2 cm of the mixture is forced into the tubing thus displacing the air and completely filling the tube. Then the stopcock is closed. The Luer Lok connection at the opposite end of the tubing is securely connected to the needle which was left in the spine. The stopcock is opened and 2 to 3 cc of the mixture is introduced into the subarachnoid space and the stopcock is closed.

With the needle left in place the patient is gently turned on his back so that the needle points downward in the center of the gap in the pad. It should not touch the table or mattress at any time. The patient should be kept in a 5 degree Trendelenburg position during the induction period. When the height of anesthesia is tested and the desired level is not obtained in ten minutes an additional injection usually of 1 cc of the solution is made. The height of the anesthesia can be extended and controlled by the following means: position of patient, volumetric dilution of anesthetic agent (barbotage), rate of injection and total dosage of drug.

Once anesthesia is obtained it is easily prolonged by small serial injections when needed and we have a set up comparable to the one existing when ether is given by the open drop method or when pentothal sodium is given by the fractional dose intravenous technique. As the anesthesia begins to wear off the fact is indicated when the intestines become less contracted, the abdominal muscles grow more tense and the

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following simple operation but most patients subjected to longer operations had no subsequent headache. Our incidence of headache is approximately 3 per cent which is about the same as we had by the former single injection method. We call attention to the fact that we had 150 consecutive cases in which there was no postoperative headache. In most instances this complaint is relieved by the use of aspirin or by lowering the head of the patient.

There is no greater incidence of *urinary retention* with this method than with the ordinary method of spinal anesthesia.

There were no motor or sensory disturbances, no cranial nerve palsies or other neurological phenomena. A number of these patients have been observed for more than three years.

There were no anesthetic deaths.

SUMMARY

1. Some of our impressions and observations are given on 1000 cases in which operation was done under continuous spinal anesthesia.

2. We have discussed the technic employed in the use of this method.

3. We wish to emphasize the controllability and safety of this method.

4. We feel that the morbidity and mortality can be lowered by the use of continuous spinal anesthesia.

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SURGICAL DIAGNOSIS IN THE MENTAL CASE

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D C SMITH MD‡

THE ever increasing tension of our times will in all probability give rise to a corresponding increase in the incidence of mental disease. Certainly we may expect an increase in the psychoneuroses and the hysterical types of disorders as well as in the precipitating causes of major psychoses with a correspondingly higher incidence of the latter. The mimicry of symptoms of true organic surgical lesions seen in mental patients often confronts the surgeon with diagnostic dilemmas which test the acumen of the best clinicians. It is not uncommon to operate upon such a patient only to find present no pathological lesion to account for the symptoms. On the other hand the chagrin is even greater when a disorder is considered to be a manifestation of the patient's mental condition and later it is proved to be organic in nature.

Errors which we have made and have seen others make in diagnosis of the presence or absence of organic lesions in the mental case have sharpened our interest in this subject. This along with the apparent increasing incidence of such cases led us to believe that it would be worth while to review a number of case histories with the hope of being able to formulate some rules which might be used to advantage in the diagnosis of surgical lesions in the patient suffering also with a diseased mental state.

To further justify our endeavor are the autopsy findings

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Case I well demonstrates the value of such an approach and a possible mechanism for the production of symptoms.

CASE I—The patient is a forty five year old white male giving a history of having had a sudden onset of crampy lower left abdominal pain accompanied by vomiting earlier in the day. He had had no bowel movements since the previous day.

Physical examination revealed a middle aged white male who appeared acutely ill with severe abdominal pain. His forehead was covered with beads of perspiration. The skin was cold and clammy. The blood pressure however was rather high (120 mm of mercury systolic and 100 diastolic). The abdomen was moderately distended. Right herniorrhaphy and appendectomy scars were present. There was marked tenderness of the entire abdomen but no definite localized rigidity. Peristalsis was hyperactive. Temperature was 98° F on admission but rose to a high as 101° F before operation.

Urinalysis was negative. White blood cells numbered 16,000 with polymorphonuclears 94 per cent lymphocytes 5 per cent and monocytes 1 per cent.

A series of films of the abdomen confirmed the clinical impression of intestinal obstruction. In several small stepladder shadows were demonstrable in the left upper and right lower quadrants.

The patient was treated symptomatically for twenty four hours with Wangenstein suction and intravenous fluids but when he failed to show any improvement an exploratory laparotomy was done. Operation revealed nothing to account for his symptoms and the abdomen was closed.

His convalescence was unremarkable except for the development of numerous other symptoms of ill health of which we established the diagnosis of a neurosis before he left the hospital.

In this case no psychiatric consideration was given until after operation. Had this been done surgery might have been avoided. It is most interesting to note how closely a functional disorder can mimic a true organic lesion. There was no evidence of a mechanical obstruction associated with an elevation of temperature and a leukocytosis. Can these findings be explained on environmental influences on the psyche leading to abnormal function of the vegetative nervous system and finally manifested in symptoms as in this case.

from our psychopathic wards covering a five year period ending December 31 1940. During this time there was a total of 13 746 admissions. There were 1634 deaths giving a mortality of 11.8 per cent. Of those patients who died 751 (45.9 per cent) were studied at autopsy. In reviewing these 751 cases we found that *surgery would have been life saving in 15 (2 per cent)* had the correct diagnosis been made before death. This 2 per cent does not include a large group of silent malignant lesions in aged patients where the cause for failure in diagnosis is obvious. Most of these patients presented acute surgical emergencies overlooked because of the masking psychosis. We feel that this figure is significant and an attempt should be made to lower it.

Importance of Psychiatric Consideration in the Surgical Patient

The psychotic patient is as much a human being as is his nonpsychotic brother but to diagnose his physical infirmities the surgeon must also be a psychiatrist of a sort himself. Such an individual can best be considered as a whole with malfunction of certain of his parts, this malfunction being in the highly specialized nervous system which is vulnerable to a great variety of environmental stimuli that are frequently overlooked by the surgeon who is accustomed to dealing only with localized organic lesions. These seemingly insignificant factors may have tremendous effect on the patient's psyche which in turn may produce a greater effect on his bodily functions and ultimately be manifested in symptom simulating organic disease. The multiplicity of scars which we see on the abdomens of mentally ill patients particularly psychoneurotics speak for themselves. The signs and symptoms which these functional disorders presented might have convinced someone as being organic in nature or the operations would never have been done. It seems that some of this unnecessary surgery could be avoided if more time was taken for psychiatric consideration of the patient instead of simply examining the region in question as is too frequently done. Ebaugh and Witt in recent papers have stressed the importance of this psychiatric adjunct to the examination of every surgical patient.

Case I well demonstrates the value of such an approach and a possible mechanism for the production of symptoms.

CASE I—The patient is a forty five year old white male giving a history of having had a sudden onset of cramps lower left abdominal pain accompanied by vomiting earlier in the day. He had had no bowel movement since the previous day.

Physical examination revealed a middle aged white male who appeared acutely ill with severe abdominal pain. His forehead was covered with beads of perspiration. The skin was cold and clammy. The blood pressure however was rather high (190 mm of mercury systolic and 100 diastolic). The abdomen was moderately distended. Right herniorrhaphy and appendectomy scars were present. There was marked tenderness of the entire abdomen but no definite localized rigidity. Peristalsis was hyperactive. Temperature was 98° F on admission but rose to as high as 101° F before operation.

Urinolysis was negative. White blood cells numbered 16,700 with polymorphonuclears 94 per cent, lymphocytes 5 per cent and monocytes 1 per cent.

A scout film of the abdomen confirmed the clinical impression of intestinal obstruction when several small stepladder shadows were demonstrable in the left upper and right lower quadrants.

The patient was treated symptomatically for twenty four hours with Wangenstein suction and intravenous fluids but when he failed to show any improvement an exploratory laparotomy was done. Operation revealed nothing to account for his symptoms and the abdomen was closed.

His convalescence was uneventful except for the development of numerous other symptoms of bizarre nature which well established the diagnosis of a neurosis before he left the hospital.

In this case no psychiatric consideration was given until after operation. Had this been done surgery might have been avoided. It is most interesting to note how closely a functional disorder can mimic a true organic lesion. There was no x-ray evidence of a mechanical obstruction associated with an elevation of temperature and a leukocytosis. Can these findings be explained on environmental influences on the psyche leading to abnormal functions of the vegetative nervous system and finally manifested in symptoms as in this case.

It seems logical since we know the higher centers are closely related to the sympathetic and parasympathetic systems and they in turn are related to intestinal motility bodily thermal control and even composition of the cellular elements of the blood. The effect that emotional disturbance may have in producing anorexia diarrhea and urinary frequency is common knowledge. Electric stimulation of areas of the monkey brain has been shown by Watts to produce simultaneous intussusception of the small intestine. If psychic disturbances and electric stimulation of the cortex can be considered to have any similarity then such a mechanism seems possible.

Case II is similar in many respects.

CASE II—A thirty year old white male was convicted and sentenced to the Philadelphia County Prison on June 11 1937 for passing a bad check. Soon after admission he attempted suicide but mental observation for a short period elicited no abnormal findings and he was permitted to return to his usual cell and to work as a clerk in the prison commissary. His course was uneventful until the night of October 11 1938 when he had an acute onset of headache and vomit. A paralysis of the left upper and lower extremities was noted on the following morning. Because of the persistence of this paralysis he was transferred to the Philadelphia General Hospital five days later with less than two months of his prison term remaining.

On admission he gave as a chief complaint a stroke of two weeks duration. Systemic review was essentially negative except for numerous gastrointestinal complaints which had been present for several years. These consisted largely of attacks of nausea and vomiting associated with gastric distention and belching which seemed to be brought on by eating greasy or fatty foods. There had been little pain associated with this except that recently he had had a feeling of soreness in the left upper quadrant. At the time of admission however he complained only of the paralysis of his left arm and leg.

Physical examination revealed flaccid paralysis of the left arm and leg along with complete sensory loss thereof. The presence of a questionable right facial paresis as the only factor which prevented making diagnosis of hysteria or even utriq;ue malingering. All laboratory studies were negative.

As time went on the patient slowly regained use of his arm and leg. On November 13 1938 he developed a tonic

and had to be catheterized 900 cc of urine being removed Cystoscopic examination on the following day revealed no cause for this sudden retention

Three days later the patient suddenly developed severe right epigastric pain with tenderness and rigidity in this area His temperature rose to 103° F Leukocyte count was 17,600 with polymorphonuclears 85 per cent and lymphocytes 15 per cent A scout film of the abdomen showed no evidence of perforated viscus but despite this a laparotomy was done immediately with a preoperative diagnosis of perforated duodenal ulcer Operation revealed no evidence of perforation or any other intra-abdominal lesion His postoperative course was totally uneventful and he was discharged back to prison in good condition

The psychiatric consultant felt that this was a case of conversional hysteria He had a great sense of guilt because of his crime and feared to face the world again He had not considered a shortening of his prison term which he was eligible for in view of his good behavior He seemed to have a sense of protection in prison which was in conflict with what would happen to him after leaving

Here was a patient who presented a series of hysterical manifestations the last of which simulated a perforated ulcer Can we again postulate psychic trauma acting through the vegetative nervous system as the explanation?

In the psychoses a somewhat different problem is encountered The psychosis instead of being obscure dominates the picture and the underlying organic disease is frequently overlooked The patient has been committed to a mental institution because of psychotic symptoms and his organic lesions are simply never diagnosed This failure in diagnosis is largely because of the lack of subjective complaints Frequently a psychotic patient will give no signs or symptoms to lead any one to suspect his being ill until he is nearly in extremis It will then be too late to render curative therapy

HISTORY

Everyone is aware of the unreliability of the history given by the psychotic patient We must not disregard his complaints however but weigh them carefully with a reliable history obtained as soon as possible after admission from

It seems logical since we know the higher centers are closely related to the sympathetic and parasympathetic systems and they in turn are related to intestinal motility bodily thermal control and even composition of the cellular elements of the blood. The effect that emotional disturbance may have in producing anorexia diarrhea and urinary frequency is common knowledge. Electric stimulation of areas of the monkey brain has been shown by Watts to produce simultaneous intussusception of the small intestine. If psychic disturbances and electric stimulation of the cortex can be considered to have any similarity then such a mechanism seems possible.

Case II is similar in many respects.

CASE II—A thirty year old white male was incarcerated and sentenced to the Philadelphia County Prison on June 11 1937 for passing a bad check. Soon after admission he attempted suicide but mental observation for a short period elicited no abnormal findings and he was permitted to return to his usual cell and to work as a clerk in the prison commissary. His course was uneventful until the night of October 11 1938 when he had a sudden onset of headache and vomiting. Paralysis of the left upper and lower extremities was noted on the following morning. Because of the persistence of this paralysis he was transferred to the Philadelphia General Hospital a few days later with less than two months of his prison term remaining.

On admission he gave as a chief complaint a triad of two weeks duration. Systemic review was essentially negative except for numerous gastro-intestinal complaints which had been present for several years. These consisted largely of attacks of nausea and vomiting associated with gastric distention and belching which seemed to be brought on by eating greasy or fatty foods. There had been little pain associated with this symptom except that recently he had had a feeling of soreness in the right upper quadrant. At the time of admission however he complained only of the paralysis of his left arm and leg.

Physical examination revealed flaccid paralysis of the left arm and leg along with a complete sensory loss of the distal portion of the extremities. Right facial pain was the only factor which prevented immediate diagnosis of hysterical venous outflow malingering. All laboratory studies were negative.

As time went on the patient slowly regained use of his arm and leg. On November 13 1938 he developed urinary retention.

den onset of such a phase in an elderly person should make one very suspicious of the development of an organic lesion. These points are well illustrated by Cases IV and V.

CASE IV—A seventy year old white female was admitted to the psychopathic ward because of a senile psychosis which had made her unmanageable at home. Five weeks prior to admission while still mentally clear she had gone to bed because of heart burn, stomach trouble and epigastric pain associated with the taking of food.

On the ward the patient gave no complaints which might lead to a suspicion of a gastro intestinal lesion. Physical examination revealed only the changes compatible with her age. Blood Kahn was negative. Blood sugar and other determinations were normal. Her course was slowly but progressively downhill. Three days prior to her death she developed a fever ranging between 98 and 101 F. Clinically death was thought to be due to bronchopneumonia superimposed upon arteriosclerotic heart failure.

Autopsy revealed the cause of death to be a perforated chronic gastric ulcer with peritonitis. Histologically there was a malignant change in the ulcer.

CASE V—An eighty year old white male had been in excellent health until six months prior to admission at which time he began to complain of epigastric pain. Three weeks before admission he developed mental symptoms with disorientation and confusion.

On admission the patient presented all the features of a senile psychosis. Physical examination disclosed the findings one would expect in a man of eighty years, the only atrophy and arteriosclerosis being the outstanding features.

Laboratory studies were not contributory.

The patient's course was accelerated with death one week after admission. Clinically death was thought to be due to general arteriosclerosis, the terminal bronchopneumonia.

Autopsy revealed death to be due to an adenocarcinoma of the stomach.

The diagnosis in both of these cases would probably have been made had more significance been placed on the patient's psychotic complaint.

some person who is in a position to give an accurate account of the events leading up to his admission. This information is of the greatest importance and should be recorded in detail. It is often of value later on despite its seeming insignificance at the time.

When there is a history of *trauma* special effort should be taken to rule out possible injury to the patient who may be seriously hurt and yet give no complaints.

CASE III—A sixty-two year old Italian male was admitted to the psychopathic ward after repeated suicidal attempts. For three weeks prior to admission he had had definite mental symptoms characterized by his threatening to kill himself and by his ordering a pay for himself only to be brought back by the police. On the day of admission he had been pulled by the police from the river near his home where he had jumped. This incident.

On admission he did not appear ill and was without complaints. His physical examination was largely negative except for blood pressure in millimeters of mercury of 200 systolic and 90 diastolic and heart sounds which were fairly regular. No areas of trauma noted.

Laboratory studies were all negative.

The patient awoke about three days with the complaints of a period of two weeks when he suddenly refused to eat. It was the first time that he was jaundiced. His stools had a green color. Temperature, pulse, and respiration were normal. The appearance of the jaundice at the first admission that he had some diagnosis. On the second admission he was brought in and admitted. With feverish condition a fever and death occurred about a week later.

Autopsy revealed death due to ruptured liver with hemorrhage in the liver and the time of his admission attempt was a day before.

Particular emphasis should be placed on the patient's *pre-psychotic complaints*. Not infrequently we see a senile type of psychosis precipitated by an organic lesion of which the patient gave typical symptoms. After the onset of the psychosis the patient no longer complains and all of our attention is focused on the psychosis. Furthermore the side

PHYSICAL EXAMINATION

Next in importance to the history is the physical examination. Psychotic patients often do not present the usual findings of a suspected disorder. The patient will often not cooperate. He may relax poorly so that evaluation of rigidity is difficult or he may not permit the examiner to get near him. Furthermore, some psychotic patients seem to have an abnormally high threshold to pain and give no indications such as by facial expression to aid in localization of the site of the trouble.

Granted that one is often confronted with problems which seem to warrant immediate surgical intervention, we believe that unless the diagnosis is unquestionable a second or even a third examination after a reasonable period depending upon the case may be of great value not only in confirming the diagnosis but in disproving it. If the findings after this postponement still point to the same diagnosis it can be given more weight. On the other hand, if the signs have shifted to another region of the abdomen, less certainty is to be placed on the original impression.

A careful and complete physical examination recorded at the time of admission not only aids in diagnosis of diseases from which the patient may be suffering at the time but may also be of great aid when the so-called emergency arises later. When the patient has a mass which apparently has become painful, we cannot question the value of knowing whether the mass was present several weeks previously when he was admitted. What was its size and appearance? Did he have a hernia and was it reducible? Routine rectal and pelvic examinations have even greater importance in the mental case because of the absence of subjective complaints.

CASE VII.—A sixty-six year old white female was admitted to the psychopathic ward with a history from her sister that she had been well until approximately five months before. At that time she developed a cold with pleurisy. The cold she stated had persisted to the time of admission. During the past few weeks it had been noticed that the patient was talking a bit queerly. In the midst of a conversation her attention would wan

The importance of the past medical history cannot be over emphasized. As in the taking of any medical history, inquiry should be made into *the nature of previous illnesses*. Often the patient will have been hospitalized elsewhere and the studies made will be most helpful.

CASE VI—A thirty three year-old white female, as admitted to the hospital with a diagnosis of schizophrenia. Soon after admission the patient complained of a great deal of epigastric pain which was attributed to a peptic ulcer. This diagnosis was substantiated by her past medical history which stated that roentgen studies in another institution had shown an ulcer years before.

The patient became progressively worse both mentally and physically. At the end of six months she was totally inaccessible socially and never conversed with anyone. Malnutrition was marked. Laboratory studies revealed an erythrocyte count of 1,800,000, hemoglobin 5 gm per 100 cc of blood, and blood carbon dioxide 78 volumes per cent. She vomited frequently but this was attributed largely to her mental status. A gastrointestinal study indicated a stenosing pyloric ulcer.

A surgical consultant who saw her felt that operative intervention was indicated on the basis of the roentgen evidence of obstruction. He, however, was skeptical and stated at the time that he would not be surprised to find no ulcer when the abdomen was opened. It was not until one month later, despite almost constant vomiting and repeated carbon dioxide determinations as high as 84 vol m per cent that operation revealed a penetrating posterior prepyloric ulcer with almost complete stenosis of the pyloric ring. A subtotal gastrectomy was done.

Postoperatively the patient improved rapidly. There was substantial mental improvement though herself was aware of it. She attributed this to the absence of pain in her stomach which had to get her down insidiously. Five weeks after operation she was placed to the custody of her sister.

Had there not been the past history of ulcer all her symptoms might have been considered a part of the psychosis. In addition, this case cautions one about the danger of disregarding the complaints of a psychotic patient. It too shows how a patient's mental symptoms may be improved by the removal of antagonizing organic lesions.

temperature varied between 99 and 101 F. Leukocyte count as 17 900 with polymorphonuclears 83 per cent lymphocytes 15 per cent and eosinophils 2 per cent. It was felt that this mass was a hydrocele with possibly a testicular tumor.

At operation eight days later a two compartment mass was found. The lower compartment was a hydrocele. The much larger solid upper compartment was found to contain a small amount of reddish brown fluid and a dense mass of dull devitalized omentum extending into the peritoneal cavity through the inguinal canal. The omentum was ligated at the external ring where it appeared to have a healthy luster. The testicle was removed and the hernia repaired. Postoperatively the patient's course became stormy and after development of an infected wound and signs of peritonitis he died on the fifth day.

Autopsy revealed death to be due to peritonitis arising from a devitalized portion of bowel which had been in the hernia.

This case shows the value of the carefully recorded admission examination or periodic examinations if the patient's stay is prolonged. The patient's record should show whether he previously had a hernia, hydrocele or other masses. Here the delay in operative therapy was because of uncertainty in diagnosis which may possibly have been avoided had his record revealed with surety his previous physical status.

LABORATORY EXAMINATIONS

As in any other type of patient the laboratory is to be used as a supplementary aid in diagnosis. The value of routine studies such as serology, blood urea and sugar determinations needs no further emphasis. Special studies must be evaluated along with the clinical picture.

We would however like to place some additional stress upon the *basal metabolic rate* when the patient's cooperation has been such that an accurate determination can be made. Hyperthyroidism or hypothyroidism is not infrequently manifest in the form of a psychosis. Recently a patient was admitted to our institution with hyperthyroidism that had produced such overactivity and mental symptoms that she had been hospitalized. One should always keep in mind this metabolic disturbance which is so easily overlooked when

der and she would begin to talk about something totally different. She too felt that the family was not treating her right.

Physical examination revealed a rather obese white female who was obviously confused and disoriented. Blood pressure in millimeters of mercury was 210 systolic and 105 diastolic. Examination was otherwise negative except for a faint apical systolic murmur and a few basal rales in the lungs.

The only abnormal laboratory finding was a leukocyte count of 27,500 with a differential count of polymorphonuclears 71 per cent, lymphocytes 2 per cent, monocytes 6 per cent and eosinophils 1 per cent.

She was diagnosed as suffering from hypertensive cardiovascular disease and a senile type of psychosis. During her nine-day course in the hospital which was rapidly downhill, she had a temperature varying between 99° and 103.8° F. Her ultimate cause of death was thought clinically to be due to a bronchopneumonia.

Autopsy revealed a small primary adenocarcinoma of the breast with widespread metastasis to the chest wall and vertebrae.

The lesson learned from this case clearly proves the value of the careful examination on admission. The patient gave prepsychotic complaints referable to the site of her disease, yet it was totally overlooked. Its discovery would have made little difference but perhaps in other cases the pathological condition would not be so extensive that helpful therapy could not be instituted.

CASE VIII—A twenty-seven-year-old white male with a diagnosis of catatonic schizophrenia had an uneventful course in the hospital for six months until he suddenly died. He had a large and some flat reddened crotal mottling. Because of the patient's mental status no information could be obtained from him. His sister, who was in the hospital, had paid no attention to anything said to him. He gave no complaints and stated that he was having pain.

Physical examination suggested a patient with firm fluctuant rostral sclerema who had no response to the glucose unit test. Drawing up and to the terminal glucose impulse could be obtained when the patient was dead. The transmittable light partially and the skin was reddened and indurated. His

of a serious illness. Intestinal obstruction will produce vomiting in the most psychotic patient. It should be thought of in every such case. Here again roentgen studies are indispensable. In doubtful confusing cases a second or even a third such study should be made after a mutual understanding has possibly been gained with the patient. As previously suggested acute mental upsets may produce changes in the gastrointestinal tract to the extent of simulating intestinal obstruction.

We are all aware of the frequency with which psychotic patients swallow *foreign bodies*. Although many theories have been proposed the cause for this is as obscure as ever. Some patients state they swallowed an object because of indigestion from which they hoped to obtain relief. Cases of morbid hunger associated with brain injuries have been reported. To carry this a bit further one might suppose that cerebral dysfunction as is no doubt present in a psychosis could produce episodes of hunger like discomfort leading to the swallowing of suitable objects within reach of the patient. We once saw a severe psychoneurotic whose chief complaint along with several others was protracted hunger. Restraint was necessary to keep him from eating while glucose tolerance tests were being done they incidentally were normal. Another patient seemed to have epileptic equivalents during which the foreign bodies were swallowed. No doubt many psychoneurotics swallow objects just to make it difficult for their caretakers but this does not explain those cases in which no one knows about the act. Moreover the patient frequently is unaware of his act despite the fact that he seemingly is sufficiently clear mentally to remember it.

CASE 1X.—A thirty year old white female had been hospitalized for seven years with a diagnosis of hebephrenic schizophrenia. Her course had been uneventful until she began suddenly to vomit without any demonstrable cause. The vomiting continued almost constantly for ten weeks all the while being treated with isolation sedation and intravenous fluids without avail. The patient became emaciated and dehydrated. Blood chlorides fell to 340 and urea nitrogen to 180. Finally a roentgenogram revealed a large spoon lying crossways in the duodenum.

masked by a psychosis. Patients suffering from myxedema usually lend themselves easily to laboratory study. Cases have been reported, however (Harward and Woods) in which the outstanding symptoms of myxedema were hallucinosis and violence. Those suffering from a psychosis in addition to hyperthyroidism more frequently will not cooperate for basal metabolic study. In such cases a trial on iodine may help confirm the diagnosis at the same time the patient is being prepared for operative therapy. Inordinate appetites with no increase in weight often call attention to an abnormal state. Such an observation may be the only clue to indicate which patients should have further laboratory study. It is well to remember, as pointed out by Bram in his large series of cases, that the incidence of mental disorder is not necessarily associated with an overly high basal metabolic rate.

ROENTGENOLOGY

Improvement in this important aid in study and its progressively increasing variety of diagnostic methods should be used to the fullest extent in the mental case as in any other. Many seemingly psychoneurotic complaints can be proved to be organic. On the other hand, the psychoneurotic may be saved from an operation if given the full advantage of roentgenological study.

The acutely psychotic patient may not cooperate for such studies as a gastro-intestinal series and barium enemas. However, the *abdominal scout film* is practical and should be employed much more than it usually is. Patients who present symptoms suggesting any possibility of a perforated viscus should receive the benefit of such studies. Air under the diaphragm can be considered a positive finding after which no delay in operation is indicated. These patients not infrequently do not complain even of a perforated ulcer and it cannot be considered an extravagance of material to make an occasional negative study. Early diagnosis has the same importance here as elsewhere in surgery.

All cases of unexplained *looming* should be carefully investigated. Too frequently this objective symptom is considered insignificant when it is really the only indication

phils 7 per cent The existence of nausea of course could not be considered because of his mental status He had not vomited Operation revealed an acute suppurative appendicitis

This case demonstrates how observation for changes in behavior is imperative if early diagnoses are to be made His behavior change was by far the outstanding symptom

Carefully recorded *temperature pulse and respiration* are even more essential in mental patients Sudden changes from their previously normal baseline should lead to an immediate explanation

CASE XI—A thirty four year old Jewish male a mongolian idiot had been taken care of by his family all his life He had had hemorrhoidectomy in our hospital one year previously at which time he had been fairly easily manageable on a surgical ward

The present illness was first suspected when a resident physician of another hospital in the city called our admission department concerning a mentally defective patient who was in their receiving ward and who appeared to be sick but was so uncooperative that examination was impossible He was accepted for transfer to our psychopathic ward for observation The only history that his father could offer was that he had been unable to manage him home for the past day as he had previously and he thought that he was sick He was on our ward for a period of three days during which time he presented no signs or symptoms suggesting an acute illness In the routine physical examination his abdomen was recorded as being normal All temperatures taken were normal with the exception of the last one before discharge which was 100 F No significance was attached to this however

On the following day the father brought the patient back with the story that he was even more unmanageable at home At this time he was obviously acutely ill The abdomen was distended peritumescence was absent and masses were palpable in the lower right quadrant He was admitted to the surgical ward but was found to be too ill to be benefited by operative intervention Supportive treatment was started under great difficulties because of his restlessness and inability to cooperate His course rapidly downhill to death within twenty four hours

In this case the patient had a sudden change in behavior and the father who had always taken care of him suspected

Duodenotomy was performed and the spirostoma removed from the second and third portions of the duodenum. The patient's convalescence was uneventful and she rapidly returned to her original state of nutrition.

Too frequently we are unwilling to give the mental patient the benefit of a diagnosis of a coincidental organic lesion and try to explain what few symptoms he does present on a functional basis. The lesson from this case alone shows very clearly that at least an abdominal scout film should be taken of every psychotic patient who develops unexplained vomiting.

DAY BY DAY OBSERVATIONS

As already stated, mental patients may not complain when they are sick and frequently are unable to give a reliable description of their ailment. Although they give no subjective symptoms one can expect their illness to manifest itself objectively by some *change in behavior*. Frequently this is the only clue to the onset of an acute illness. If we expect to make early diagnoses or diagnoses at all, we must make use of all possible objective findings and observations. The nurse or attendant in charge should be instructed to report any sudden change in a patient's behavior. They are most familiar with each patient and in a position to best recognize behavior which is abnormal for that particular patient.

CASE V.—A fifteen-year-old child developed frequent schizophrenic attacks. On the month after admission he was sent to the Straubel and Hospital of the Pennsylvania State University for examination. The first examination revealed normal abdominal temperature of 98° F. He became most cooperative and constant about the first of the following month and found the series of questions. When he began to fight with the patients it became necessary to restrain him. A surgical consultant saw the patient and advised that he should be operated on as indicated. The patient refused to be operated on. He was then mentally hospitalized in the light of the fact that he had leukocytosis with 11,100 white blood cells. The differential count of peripheral blood showed 54 per cent lymphocytes and 44 per cent neutrophils.

As our case records reveal the first indication of a serious illness in a psychotic patient frequently is a change in behavior. These behavior changes can best be detected by the nurse or attendant in charge who knows the patients best. Perhaps the most important single factor in the early diagnosis of surgical lesions in the mental case is careful observation for behavior which is not normal for that patient.

something was wrong. Three days' observation failed to lead us to a diagnosis of an acute abdominal condition which he must have been suffering from as evidenced by the elevation of temperature (100° F.) taken just before discharge.

A patient's sudden *refusal to eat* may have significance when he has previously eaten with regularity. *Changes in bowel habit* are to be watched for. Blood in the stool or change in color has the same import here as elsewhere, but the patient is unable to make the observation. *Vomiting*, as previously mentioned, should always be considered a danger signal; its occurrence reported immediately to the physician in charge.

SUMMARY

Because of the apparent increase in mental disorders and the difficulty encountered in making diagnosis of associated organic lesions, we present the study of several case histories from the wards of the Philadelphia General Hospital with the hope of being able to formulate a somewhat systematized method of diagnosis which might be used to advantage in lowering the morbidity and mortality in such cases.

The surgeon must be his own psychiatrist if he hopes not to fall a prey to the alluring complaints of the psychoneurotic patient. Modern methods of diagnosis are to be used to their fullest extent to prove the presence or absence of organic lesions which are frequently mimicked by manifestations of these functional disorders.

Patients suffering from psychoses frequently do not present the usual findings of a suspected organic lesion; the symptoms of which are completely masked by the mental picture. A history from the very beginning of the patient's illness is to be obtained from a reliable source as soon after admission as possible. Particular stress is to be placed upon past medical history and prepsychotic complaints. A carefully recorded admission physical examination may be of great value later when the so-called emergency arises. The laboratory should be used as a supplementary aid as elsewhere in medical diagnosis. *Roentgenographic studies, especially the abdominal scout film, have been shown to be of tremendous aid and the indications for their use are many.*

THE CONTROL OF FLUID BALANCE BY LABORATORY METHODS

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THE maintenance of normal fluid balance in surgical patients requires careful control by laboratory methods. Thus the condition of the patient may be evaluated by considering the nature and degree of chemical imbalance. Variations observed in the chemical composition of the patient's blood indicate the kind of parenteral fluid needed. These data are useful in calculating the dose of fluids required. However in all other phases of scientific medicine the laboratory findings must be intimately correlated with the clinical picture.

The fundamental considerations of fluid balance have been reviewed many times and will not be repeated here. The subject involves a consideration of water, electrolytes and plasma proteins. As first clearly expressed by the group at Ann Arbor, the surgical patient must have sufficient water to cover the insensible loss from 1 to 3 liters daily, as well as water to provide for a liter of urine per day. 3 or 4 gm of sodium chloride must be given to cover the daily urinary loss and in addition to the basic needs abnormal fluid loss should be replaced by an equal volume of 0.85 per cent sodium chloride solution. The importance of plasma protein levels has been emphasized by other investigators. Certain changes in hemoconcentration indicate disturbances in the fluid balance. The ability of the kidneys to maintain normal fluid balance has been implied by tacit assumption. In the presence

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each patient. Examples of the methods for calculating the requirements will be given in the following section.

The *proper dose* of parenteral fluids is just as important as is the dose of any powerful drug. Generalized edema may result from an overdose of fluid, especially in a patient with renal insufficiency. Pulmonary edema is an ever present danger of too much parenteral fluid and circulatory embarrassment may occur in the patient with a poor cardiac reserve. On the other hand, no advantage is gained by giving a patient 100 cc. of plasma when the dose needed is 1500 cc. Half a liter of saline is of little benefit to a dehydrated patient who needs 3 liters of saline plus a liter of lactate solution. A quantitative correction of acidosis should be attempted. In the majority of cases the correct dose of parenteral fluids can be calculated quite accurately.

EVALUATION OF THE PATIENT

In the control of fluid balance, laboratory determinations mean little unless they are considered in relation to the patient's *history* and *physical findings*. In many instances the program of fluid administration must be modified in the light of physical findings. Any symptoms of cardiovascular or renal disease should be noted and its nature determined. The severity of the disease should be evaluated quantitatively and its probable influence on the fluid balance program appraised. The nature and severity of traumatic injuries and surgical procedures influence the program. There should be a record of abnormal fluid losses: vomiting or gastric drainage, biliary drainage, diarrheal stools, blood loss as visible or hidden hemorrhage and serous ooze. Accurate estimates of intake and output, especially the urine volume, are important.

In the *physical examination* all evidence of dehydration should be noted carefully. The appearance of the skin, mucous membranes and eyes is significant. Severe acidosis is usually accompanied by shallow rapid respirations, red lips and a fruitlike odor on the breath. Pale, cold extremities and a feeble pulse suggest a reduction in peripheral blood flow. This may be the result of a diminished blood volume and precede the onset of shock. Obvious edema may be associ-

of seriously impaired renal function however the precise control of electrolyte and water balance becomes well nigh impossible

This paper based upon experience gained in the study of more than 600 patients who presented problems in fluid balance at the Pennsylvania Hospital will stress three points (1) the simplicity of the laboratory methods used in the control of fluid balance (2) the individual consideration of each constituent in parenteral fluids i. e. water sodium chloride plasma protein etc. as separate entities and (3) the importance of quantitative dosage of parenteral fluids

The laboratory methods may be limited to a few routine determinations requiring a minimum of special equipment and technical ability. From specific gravities of plasma which may be readily measured by the falling drop method or by direct weighing of the samples in special micro pipettes on a rapid chainomatic balance plasma protein concentrations can be calculated. Plasma protein concentrations can be obtained by employing the biuret reaction as modified by Kingsley. This photo electric method is in some respects more trustworthy than the specific gravity method. Plasma chlorides are titrated in tungstic acid filtrates or in nitric acid digests. Plasma carbon dioxide combining power is determined by the volumetric method. Serial hematocrit determinations made on heparinized blood in the Sanford Magath tube provide enough plasma for the other analyses and also measure changes in hemoconcentration. In patients with renal insufficiency the blood urea nitrogen must be determined at frequent intervals.

In a satisfactory program of fluid balance control the requirement for a patient must be broken down into the requirement for each individual constituent of the parenteral fluids namely water sodium chloride alkali as sodium lactate or sodium bicarbonate and plasma protein. Whereas sodium chloride in 0.85 per cent solution may be quite satisfactory for one patient another may require water as 5 per cent glucose intravenously sodium lactate in one sixth molar solution and some plasma protein. The requirements vary for

mal indicate a need for saline in most cases. The total base concentration may be calculated from the plasma carbon dioxide combining power and plasma chloride concentration by converting these figures to milliequivalents per liter (M eq/L) and adding 25 M eq/L for the remaining acid radicals as follows:

$$\begin{aligned} \text{CO}_2 \text{ mb m g p c} &= 60 \text{ m p c} \times 0.45 = 27 \text{ M eq/L} \\ \text{Chl rides (as N Cl)} &= 600 \text{ mg p c} \times 0.17 = 102 \text{ M eq/L} \\ \text{R (HPO}_4\text{ SO}_4\text{ g c d p c)} &= 25 \text{ M eq/L} \\ \text{Total acid} &= 27 + 102 = 129 \text{ M eq/L} \end{aligned}$$

Specimens of urine collected at the same time as the blood sample should be examined for albumin and acetone and in the absence of evidence of marked renal damage ketosis or hypoproteinemia R may be assumed to equal about 25 M eq/L.³ The resultant figure for total base although not absolutely correct is sufficiently accurate for most clinical purposes.

Plasma protein levels are determined at frequent intervals daily in patients with peritonitis empyema a severe burn or other conditions in which protein leaks out of the vascular tree. The plasma protein level must be kept above 6 gm per 100 cc to maintain a normal distribution of fluid between the blood stream and tissues and to prevent local edema and the delayed healing of wounds. The protein level should be considered in relation to the hematocrit value. A rising hematocrit value and a constant protein level indicate a loss of protein from the main stream of the circulation. A falling plasma protein level with a rising hematocrit value indicates a very serious loss of protein such as is usually seen in severe burns and untreated peritonitis.

CLINICAL CONDITIONS

Daily Requirements of Water and Salt

For the average adult between 2 and 3 liters of water must be allowed every twenty-four hours. This will cover the insensible loss of water from the skin and lungs and also pro-

Correct factors for high humidity will not mill-eq l ts

ated with excessive fluid administration a low plasma protein level renal insufficiency mechanical interference with circulation or with other factors. Pulmonary edema is an ominous development. Physical examinations must be repeated at frequent intervals because an immediate change in the program must be made at the appearance of any adverse reaction.

The laboratory methods previously mentioned are useful in evaluating the state of hydration electrolyte balance plasma protein level and the need for red cells. Abnormal changes in hydration of the body as a whole are usually reflected by alterations in the specific gravity of whole blood or plasma. The hematocrit value is another excellent measure of hemoconcentration especially when plasma protein levels are determined simultaneously. Serial hematocrit values made at frequent intervals show grossly the total amount of fluid needed by the patient. In severe burns uncomplicated by hemorrhage the hematocrit values may be used in calculating the plasma loss (see discussion below). At the onset of surgical shock hemoconcentration usually precedes the appearance of the clinical signs. Hence effective treatment for shock must be started in the early stages in the period of hemoconcentration detectable only by laboratory method and prior to the appearance of clinical symptoms. In severe hemorrhage with hemodilution early treatment must be instituted to prevent the onset of shock and circulatory collapse.

The more important changes in the electrolyte may be followed by routine determination of the plasma carbon dioxide combining power and chloride levels. Values in carbon dioxide combining power above 80 volumes per cent indicate a marked alkalemia; values between 55 and 75 indicate a moderate degree of acidosis; values below 55 indicate a serious degree of acidosis needing immediate treatment with alkali. Further information on the nature of the acidosis is shown by a plasma acetone test. The sodium chloride concentration of the plasma should be within the normal range 580 to 600 mg. per 100 cc. Higher values suggest excessive saline administration or renal insufficiency. Values below nor-

and plasma protein levels. However the results of these determinations are not readily translated into the dose of fluid required to restore a normal state of dehydration. The formulas suggested for this calculation have not proved entirely satisfactory and must be revised before being recommended for general use.

Acidosis

The accumulation of acids in the extracellular fluids of the body can be measured by the carbon dioxide combining power of the plasma. The presence of acetone in the plasma indicates an acidosis due to organic acids as is usually seen in dehydration, starvation or diabetes mellitus. If the carbon dioxide combining power is about 45 volumes per cent, 1 liter of 5 per cent dextrose in saline is an adequate dose for an adult weighing 70 kilograms (154 pounds). If the carbon dioxide combining power is 35 volumes per cent, 2 liters of 5 per cent dextrose in saline are needed in addition to the daily requirement. If the carbon dioxide combining power falls below 35 volumes per cent, alkali in the form of sodium bicarbonate or sodium lactate should be given along with the saline. The calculated dose of sodium bicarbonate for a person weighing 70 kilograms is 0.5 gm (7½ grains) for each point the carbon dioxide combining power is below 35. For example, a patient weighing 70 kilograms with a carbon dioxide combining power of 15 volumes per cent will need 0.5 times (35 - 15) or 10 gm of sodium bicarbonate plus 2 liters of saline. This dose should be varied with the weight of the patient. If the carbon dioxide combining power does not return to normal in twelve hours the bicarbonate is repeated. For each gram of sodium bicarbonate 72 cc of one sixth molar sodium lactate solution may be substituted.

An alternate treatment for acidosis is used in many clinics and at times by the present authors. Enough alkali to restore the carbon dioxide combining power to normal is given without dextrose or saline. The dose of sodium bicarbonate for a patient weighing 70 kilograms is 0.5 gm for each point the carbon dioxide combining power is below 55 volumes per cent. For example, with a carbon dioxide combining power

vide for a liter or more of urine. Elevation of temperature will increase the insensible loss. For each degree Fahrenheit above normal the daily requirement is increased by 750 cc. In addition to water the patient on parenteral feedings should have 3 to 5 gm of sodium chloride daily or 500 cc of 0.85 per cent saline. This requirement for water and salt is basic and must be given in addition to the indicated dose for rehydration, correction of acidosis and so on. Both water and salt should be given by mouth whenever possible.

D hyd +

A negative water balance resulting from excessive loss or inadequate intake can be corrected in a semiquantitative manner. The degree of dehydration may be estimated either by clinical observation or by laboratory methods. As to the former the authors recommend their two-four-six rule. Depending upon the degree of dehydration fluid equal to 2, 4 or 6 per cent of the body weight is given. Patients with slight dehydration as characterized by a marked thirst, some dryness of mucous membranes and a urine with a high specific gravity totaling 500 or 600 cc per day require fluids equal to 2 per cent of the body weight. Those with moderate dehydration having a pronounced dryness of mucous membranes, a dry skin and urine volumes of 200 or 300 cc per day require fluid equal to 4 per cent of the body weight. Finally those with severe dehydration indicated by decreases in intra ocular pressure, a very dry skin that stands up when pinched into a fold, little or no urine and sometimes coma require fluids equal to 6 per cent of the body weight. If the fluids can be given by mouth, salty broth and citrus fruit juices will suffice. Isotonic sodium chloride solution can be given subcutaneously. For the intravenous route a mixture consisting of three parts of 0.85 per cent sodium chloride and one part of one sixth molar sodium lactate is the ideal solution. When acidosis accompanies the dehydration the amount of lactate is increased but the total volume of fluid remains the same.

The degree of dehydration may be determined by the specific gravity of the blood changes in the hematocrit value

If this quantity of sodium chloride is given intravenously as isotonic solution the tissues will be rehydrated and the chlorides will be restored to normal. An efficient kidney will eliminate the excess sodium as bicarbonate in an alkaline urine. In this case the daily requirement for water should be given as 5 per cent dextrose solution.

If laboratory data are not available treatment should be guided by the clinical rule of Coller and associates. The net volume of gastric drainage fluid should be replaced with an equal volume of isotonic saline given intravenously.

Biliary Drainage

Secretions which pass through the common duct are alkaline in reaction and contain more base (sodium) than any other ion. The loss of these secretions by external drainage results in a serious depletion of base, dehydration and acidosis. The extent of the sodium deficit can be calculated from the equation proposed by Elkinton, Gilmour and Wolff:

$$G + N + q - d - 0.0046 W \times \left(155 - \frac{(100-H) H B}{(100-H) H} \right)$$

$$\begin{aligned} W &= \text{body weight in kg} \\ H &= \text{hematocrit} \\ H &= \text{hematocrit} \\ B &= \text{base deficit in mEq/L} \end{aligned}$$

The sodium ion requirement can be converted into grams of sodium chloride, sodium bicarbonate or sodium lactate by the factors 2.5, 3.6 and 4.9 respectively. After the sodium requirement and its equivalent in liters of isotonic saline or lactate solution is calculated the program of treatment is planned. The acidosis is corrected with the proper volume of sodium lactate and the remainder of the sodium requirement is given as three parts isotonic saline plus one part of one sixth molar sodium lactate solution. An hour or so after the infusion of fluids is completed chemical analyses on the plasma are repeated to make sure that the imbalance has been corrected.

Diet

In addition to water losses in liquid stools a large quantity of sodium chloride and some bicarbonate is lost from the

of 15 volumes per cent the dose of sodium bicarbonate for the patient weighing 70 kilograms is 0.5 times (55 - 15) or

0 gm. The required weight of bicarbonate is taken from a clean new package dissolved in sterile pyrogen free water to make a 3 or 5 per cent solution and given intravenously. Some dangers arise in the preparation of sodium bicarbonate for intravenous use a procedure which should be undertaken only where experienced personnel and adequate equipment are available. Commercially prepared sodium lactate solutions may be used safely in almost any clinic.

Acidosis due to renal insufficiency is characterized by the absence of acetone and a high serum inorganic phosphate level frequently 10 or 15 mg of phosphorus per 100 cc. It is very refractory to treatment. The calculated dose of alkali seldom raises the carbon dioxide combining power to the expected figure. The dose must be repeated daily for two or three days to correct the acidosis. Because of the renal insufficiency considerable caution should be exercised in giving alkali or saline to this type of patient for large amounts of sodium may be retained and produce a massive edema.

G a s t r o n g

The continued loss of gastric juice may result from pernicious vomiting, high intestinal obstruction with vomiting or gastric drainage through suction tubes. The chemical imbalance is the same in each case with dehydration, alkalosis and hypochloremia. The plasma carbon dioxide combining power rises to 80 or 90 volumes per cent and the chloride falls to below 300 mg of sodium chloride per 100 cc. Symptoms of dehydration are rather marked. Treatment is simple and effective if renal function is normal. Chlorides may be restored to normal with a dose of sodium chloride calculated by the *Coller Maddock rule* which is 0.5 gm of sodium chloride per kilogram of body weight for each 100 mg per 100 cc that the plasma chlorides must be raised to reach 560 mg per 100 cc. For example, eight if patient is 70 kilograms, plasma chlorides 410 mg per 100 cc

$$\text{NaCl d} = 0.5 \times 0 \frac{560 - 410}{100} = 5.5 \text{ gm}$$

If this quantity of sodium chloride is given intravenously as isotonic solution the tissues will be rehydrated and the chlorides will be restored to normal. An efficient kidney will eliminate the excess sodium as bicarbonate in an alkaline urine. In this case the daily requirement for water should be given as 5 per cent dextrose solution.

If laboratory data are not available treatment should be guided by the clinical rule of Coller and associates. The net volume of gastric drainage fluid should be replaced with an equal volume of isotonic saline given intravenously.

Binary Diagram

Secretions which pass through the common duct are alkaline in reaction and contain more base (sodium) than any other ion. The loss of these secretions by external drainage results in a serious depletion of base, dehydration and acidosis. The extent of the sodium deficit can be calculated from the equation proposed by Elkinton, Gilmour and Wolff:

$$\text{Gm Na} + q \text{ d} = 0.0046 W \times \left(155 - \frac{(100 - H) H B}{(100 - H) H} \right)$$

$$\begin{array}{l} W = \text{body weight in kg} \\ H = \text{serum sodium in mEq/L} \\ H = \text{pH} \\ B = \text{base deficit} \end{array}$$

The sodium ion requirement can be converted into grams of sodium chloride, sodium bicarbonate or sodium lactate by the factors 5.36 and 4.9 respectively. After the sodium requirement and its equivalent in liters of isotonic saline or lactate solution is calculated the program of treatment is planned. The acidosis is corrected with the proper volume of sodium lactate and the remainder of the sodium requirement is given as three parts isotonic saline plus one part of one sixth molar sodium lactate solution. An hour or so after the infusion of fluids is completed chemical analyses on the plasma are repeated to make sure that the imbalance has been corrected.

Diet

In addition to water losses in liquid stools a large quantity of sodium chloride and some bicarbonate is lost from the

body. The net result is dehydration and acidosis with salt depletion. In certain patients, particularly children, ketosis appears. Treatment for these conditions is the same as outlined above. Hard candy by mouth or 5 per cent dextrose in saline will clear up the ketosis in most cases. Salty broths or gruel by mouth will help cover the high requirement for sodium chloride.

The large amount of fluid lost externally through an ileostomy has the same systemic effect as diarrhea. The fluid balance program is directed at the control of acidosis, dehydration, and salt depletion. Giving large amounts of drinking water without ample salt intake is to be discouraged. The water literally washes out sodium chloride and further depletes the salt already inadequate in amount.

Severe Burns

The fluid imbalance in severe burns is intimately related to the extravasation of plasma protein. Thermal trauma alters the capillary bed in the burned area so that large quantities of plasma leak into the tissues or to the surface. In a third degree burn involving 70 to 80 per cent of the body surface, nearly half the total plasma protein will escape from the vascular tree within eight to twelve hours following the burn. The resulting hemoconcentration is due to an abnormal distribution of fluids and a serious disturbance in the mechanism for controlling the distribution. Contrary to views formerly held, the burned patient is not dehydrated and does not need large quantities of saline. The rational treatment of this condition is *massive plasma transfusions* sufficient to restore the depleted plasma volume, improve the peripheral circulation, and prevent the onset of burn shock. Two questions arise: When to give plasma and how much to give. Studies reported elsewhere have shown that proteins continue to leak out of the capillaries for some forty or fifty hours. Large amounts of plasma given during this time are lost into the tissue. However, during this period it is necessary to give small amounts of plasma to prevent the development of burn shock.

In one series of patients (service of Dr. Walter Estell Lee) the plasma requirement varied from 25 to 100 cc per hour.

for adults. The hematocrit value was kept below 55 per cent cells and the plasma protein above 6 gm per 100 cc. A continuous infusion of plasma was more effective than single doses repeated at six or twelve hour intervals. This program insured the maintenance of peripheral circulation as indicated by a fair pulse volume at the wrist and ankle. After the capillaries recovered sufficiently to prevent leakage of the plasma protein usually some forty hours after the burn the plasma volume was restored to normal by a large transfusion of plasma.

The amount of plasma needed at this time can be calculated from the body weight, hematocrit value and plasma protein level by the equation given at the top of Fig. 531. To simplify the use of this equation the chart (Fig. 531) has been constructed for an adult 70 kilograms (154 pounds) body weight with a basal or normal hematocrit value of 45 per cent cells and a normal plasma protein level of 7 gm per 100 cc. Hematocrit values are plotted as the base line, plasma protein deficits as the left hand vertical margin, equivalent plasma volumes as the right vertical margin, and plasma protein levels as the curves. To read the plasma deficit for a burned patient take the point at which the vertical line corresponding to the hematocrit value intersects with the line representing the plasma protein level (interpolating when necessary). Horizontally opposite this point at the right margin is the deficit in volume of normal plasma, and at the left the deficit in grams of plasma protein. For a further discussion of this chart see the original paper.

In addition to the plasma leakage the burned patient shows more or less disturbance in the electrolytes. A mild acidosis appearing during the first twenty four or forty eight hours can be corrected with the calculated volume of one sixth molar sodium lactate solution. Sweetened fruit juices by mouth or 10 per cent dextrose intravenously will aid in controlling the acidosis and maintain a high liver glycogen. Any tendency toward hypochloremia is counteracted by the administration of isotonic saline. The total volume of fluid including plasma should not exceed 3 or 4 liters per day during the first two days.

CALCULATED PLASMA PROTEIN DEFICIT IN SEVERE BURNS

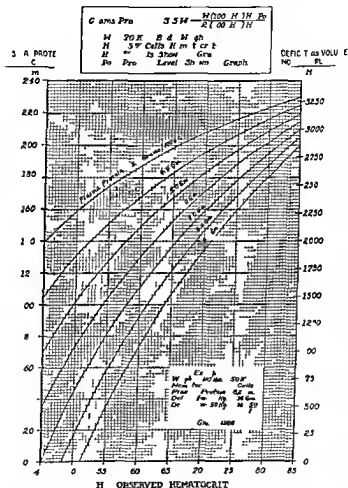


Fig 531--(R p d d f m W lff d L A l f S g ry J
 194 by permiss f h p bl hrs J B L pp α Co Ph l d lph
 P)

P t t

The existence of extensive peritonitis is usually associated with three chemical lesions hypoproteinemia dehydration and acidosis. A fluid rich in protein passes from the vascular tree into the abdominal cavity thereby reducing the plasma protein. The elevated temperature increases the basic requirement for water and steps up the general metabolic activity. The treatment is illustrated by a patient showing the following data:

B d	gh	0 k l g m	(154 p d)
T mp	rato	(m h)	103 F
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U	l m	24 h	210
Ca d	l	v t m	d k l v f m l p p
ll			

The requirements for this patient are calculated as follows. The basic water requirement is 2500 cc per day plus 1250 cc needed because of the fever (5 F). This should include 500 cc of saline to cover the normal loss of chlorides in the urine and sweat. Rehydration of tissues will require 800 cc (4 per cent of body weight) to be given as 2100 cc isotonic saline and 700 cc of one sixth molar sodium lactate solution. Raising the carbon dioxide combining power with alkali need not be attempted in this case. One liter of 5 per cent dextrose in saline is preferable although 2 liters might be given. The plasma protein deficit is 1500 cc of normal plasma as read from Fig. 531. Half this dose should be given at once and the remainder on the following day to spread out the burden on the cardiovascular system. The total fluid requirement is the basic water need plus the allowance for the elevated temperature and rehydration of the tissues or a total of 6550 cc. The saline lactate and plasma are included as parts of this volume. The fluid dose recommended for the first twenty-four hours is:

Sal	0.85 pe	3100 cc
Al 6 x d	l et	00
N m 1 pl		750
D	t 10 pe	000
T	l fl t	6550 cc

During the second twenty four hour period of treatment the remainder of the plasma dose is given with 500 cc of saline and sufficient dextrose solution to make a total volume of 3750 cc. If the carbon dioxide combining power does not return to normal on the second day an additional liter of dextrose in saline should be given.

Plasmorydynia

Fluids from a lung abscess, empyema or following a pneumonectomy or lobectomy are rich in protein which come initially from the plasma. Long continued loss of these fluids leads to a depletion of plasma proteins with a possible reduction in plasma volume. The situation is aggravated because the chronically diseased lung usually occurs in a debilitated individual who may not have a normal capacity to regenerate plasma protein. In view of the wide variations among patients no general rules can be given. Small repeated transfusions (100 or 200 cc) of normal plasma should be given once or twice weekly if the plasma protein is less than 6 gm per 100 cc or the hematocrit value is above normal.

Shock and Hemorrhage

In both of these conditions the critical state is a consequence of disparity between the volume of circulating blood and the capacity of the vascular tree. The immediate treatment needed is a restoration of blood volume by massive transfusions of plasma or whole blood. In view of the current controversies regarding the validity of laboratory data in shock and hemorrhage reliance should be put on clinical indications. If there is no perceptible pulse at the ankle or wrist 500 to 1000 cc of plasma should be given rapidly—within half an hour. Additional plasma or whole blood is then given slowly about 100 cc per hour until a peripheral pulse is maintained in fair volume. The red cell count may be raised in an average size adult about one million by giving 1 liter of whole blood. In treating the patient in shock restoring and maintaining the total blood volume is more important than getting a normal red cell count.

SUMMARY

The successful control of fluid balance in surgical patients is conditioned by three factors (1) intimate cooperation between clinical and laboratory staffs (2) the supply of suitable parenteral fluids including an adequate stock of human blood and plasma (blood bank) and (3) systematic study and treatment of each patient as an individual problem in fluid balance

A routine program for the study and control requires

- 1 History and physical examination of the patient
- 2 Urinalysis determination of hematocrit values blood plasma chlorides protein and carbon dioxide combining power and blood nonprotein nitrogen or urea nitrogen
- 3 The proper interpretation of the findings clinical and chemical in order to determine the nature of the chemical lesion and recognize the limiting factors involved
- 4 A plan for treatment covering (a) the kind of fluids to be given and the route of administration (b) the dose of each required (c) the administration of the fluid and (d) the indications of untoward reactions and finally
- 5 Checking the results of treatment by clinical impressions and by repeating the laboratory tests

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